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Real-world tyrosine kinase inhibitor treatment pathways, monitoring patterns and responses in patients with chronic myeloid leukaemia in the United Kingdom: the UK TARGET CML study

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Abstract

Management of chronic myeloid leukaemia (CML) has recently undergone dramatic changes, prompting the European LeukemiaNet (ELN) to issue recommendations in 2013; however, it remains unclear whether real-world CML management is consistent with these goals. We report results of UK TARGET CML, a retrospective observational study of 257 patients with chronic-phase CML prescribed a first-line TKI between 2013 and 2017, most of whom received first-line imatinib (n=203). Although 44% of patients required ≥1 change of TKI, these real-world data revealed that molecular assessments were frequently missed, 23% of patients with ELN-defined treatment failure did not switch TKI and kinase domain mutation analysis was performed in only 49% of patients who switched TKI for resistance. Major molecular response (MMR; *BCR-ABL1*^{IS} ≤0.1%) and deep molecular response (DMR; *BCR-ABL1*^{IS} ≤0.01%) were observed in 50% and 29%, respectively, of patients treated with first-line imatinib and 63% and 54% receiving a second-generation TKI first line. MMR and DMR were also observed in 77% and 44% of evaluable patients with ≥13 months' follow-up receiving a second-generation TKI second line. We found little evidence that cardiovascular risk factors were considered during TKI management. These findings highlight key areas for improvement in providing optimal care to patients with CML.

Keywords: tyrosine kinase inhibitor, chronic myeloid leukaemia, real-world study, molecular response, management

Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionised outcomes for patients with chronic myeloid leukaemia in chronic phase (CML-CP), with survival rates approaching those of the general population (Bower *et al*, 2016; Hoglund *et al*, 2013; Sasaki *et al*, 2015). Consequently, key considerations for optimal patient care have evolved considerably. While the primary aim remains achievement of molecular response that minimises the risk of disease progression (Baccarani *et al*, 2013), increasingly, complications of the treatment need to be considered. It is therefore essential for physicians to understand the best use of the available ABL1-targeting TKIs (Baccarani *et al*, 2013). This is the principal purpose of the 2013 European LeukemiaNet (ELN) recommendations, which increased focus on molecular responses at 3, 6 and 12 months, with patients' responses categorized as optimal, warning or failure (Baccarani *et al*, 2013). Patients experiencing failure are at particular risk of disease progression, and the guidelines recommend that such patients switch treatment and undergo assessment for *BCR-ABL1* kinase domain mutations (Baccarani *et al*, 2013).

While the ELN 2013 guidelines state that patients must achieve a major molecular response (MMR; *BCR-ABL1* ≤0.1% on the International Scale [IS]) by 12 months for their response to be considered optimal (Baccarani *et al*, 2013), deeper levels of response, including MR^4 (*BCR-ABL1*^{IS} ≤0.01%) and $MR^{4.5}$ (*BCR-ABL1*^{IS} ≤0.0032%), are also recognized as important milestones (Cross *et al*, 2012; Etienne *et al*, 2014; Hehlmann *et al*, 2014). Some patients with a sustained deep molecular response (DMR; MR^4 or better) may be eligible to attempt treatment-free remission (TFR) (Hochhaus *et al*, 2017b; Mahon, 2017; NCCN, 2020; Rea *et al*, 2018). Clinical trials have demonstrated that patients are more likely to achieve optimal and deeper

responses to first-line therapy at key ELN milestones when second-generation (2G) TKIs are used rather than imatinib; however, achievement of responses in real-world practice is less well studied, particularly in the second-line setting (Cortes *et al,* 2018a; Cortes *et al*, 2016; Hochhaus *et al*, 2016). Achievement of ELN-defined responses and how ELN guidelines are implemented in real-world settings are infrequently explored.

An increased risk of cardiovascular (CV) adverse events (AEs) has been described in patients receiving 2G- or third-generation–TKIs compared with imatinib, especially in patients with pre-existing CV risk factors (Chai-Adisaksopha *et al*, 2016; Cortes *et al*, 2018b; Cortes *et al*, 2016; Hochhaus *et al*, 2016; Lipton *et al*, 2016). Given the excellent long-term outcomes in CML, comorbidities are now a major consideration (Jabbour *et al*, 2014; Saussele *et al*, 2015). However, in UK routine clinical practice, it is unclear how physicians assess and manage CV risk factors or how CV risk factors affect TKI management.

UK TARGET CML (CAMN107CGB12) is a retrospective observational study of baseline assessment of patients with CML-CP, TKI treatment pathways, response monitoring patterns and response rates in routine UK National Health Service (NHS) clinical practice; we compared findings with ELN 2013 recommendations (Baccarani *et al*, 2013).

Methods

Study design

This retrospective noninterventional study was conducted at 21 UK NHS secondary and tertiary care centres. Data were collected from paper and electronic records. Inclusion criteria included

CML-CP diagnosis at start of first-line TKI, age ≥18 years and ≥6 months of follow-up from date of first TKI (between January 2013 and April 2017). Patients prescribed first TKI in a clinical trial and patients in accelerated phase (AP) or blast phase (BP) before initiation of first TKI were excluded.

Objectives were to describe TKI treatment pathways in the UK, patient characteristics, practices for assessing and managing CV risk factors before TKI treatment, responses to first- and second-line TKI therapy at ELN time points, recorded reasons for stopping/changing TKIs, adherence to ELN 2013 recommendations and disease progression frequency and management. AE data were not collected.

Data were analysed using descriptive statistics, with a cutoff date of June 6, 2018, using Microsoft Excel and STATA (version 13; StataCorp LLC, College Station, TX, USA). A study size of 200-250 patients in approximately 20 centres (maximum of 40 patients/centre) was expected to give a representative sample of patients in the UK and provide reliable quantitative and qualitative variables.

For comparison with ELN, where data were available, responses were categorised as optimal, warning or failure according to ELN 2013 recommendations (Baccarani *et al*, 2013). If *BCR-ABL1* transcript levels were not available on the IS, unconverted *BCR-ABL1*/*ABL1* percentages were used to reflect real-world practices at that centre (all centres used *ABL1* as a reference gene). Two of 14 centres (14%) reported on the IS in 2013; increasing to 17/21 (81%) in 2017.

Results

Patient demographics and baseline characteristics

Two-hundred-fifty-seven patients (186 from 14 tertiary centres and 71 from 7 general hospitals) were enrolled between November 2015 and September 2017. Median follow-up by the data cutoff was 32.9 months (range, 12.6-58.6). Baseline characteristics are shown in **Table I**. Clinical characteristics (other than white blood cell counts) and risk scores at diagnosis were not well documented.

The first-line TKI was imatinib in the majority of patients (79%); reasons for first-line TKI choice were recorded for <50% of patients: clinician preference, "standard first-line choice" and "good results expected" were the most frequently cited reasons (**Supplementary Table I**). First-line imatinib and 2G-TKIs were prescribed to 31/42 (74%) and 11/42 (26%) patients with high Sokal scores, respectively, and 23/34 (68%) and 11/34 (32%) with high European Treatment and Outcomes Study (EUTOS) scores. Patients receiving a first-line 2G-TKI were younger (median, 46 years [95% CI, 41-53 years] than those receiving first-line imatinib (median, 55 years [95% CI, 52-59 years]; Mann-Whitney U test, $P = 0.0128$).

CV risk factors and other documented comorbidities at baseline

Among all patients, 149 (58%) had ≥1 recorded comorbidity at baseline (**Table I**). Seventy-four patients (36%) receiving imatinib had CV comorbidities at baseline vs 7 (13%) receiving a 2G-TKI (**Table II**). Only 74 patients (29%) had baseline blood pressure documented; 33 (45%) had stage ≥2 hypertension (**Supplementary Table II**) (Whelton *et al*, 2018).

Exact levels of baseline blood glucose were documented in 58 patients (23%); documentation occurred more often in patients treated with first-line 2G-TKI (20/54 [37%]) vs imatinib (38/203 [19%]). Baseline low-density lipoprotein and total cholesterol levels were recorded in 23 (9%) and 40 (16%) patients. CV risk assessment tool use was documented for 10 patients (4%), with the validated QRISK2 tool used in 3 (1%).

Response monitoring practices

Within 12 months of starting first-line TKI, 250 patients (97%) had ≥1 real-time quantitative polymerase chain reaction (RQ-PCR) assessment and 221 patients (86%) had ≥3 RQ-PCR assessments. Two-hundred-four (79%), 177 (69%), and 162 (63%) patients had assessments at the 3-, 6-, or 12-month ELN milestones (regardless of TKI line), respectively. Cytogenetic testing (chromosome banding analysis or fluorescence in situ hybridization) was conducted less frequently. Frequency of assessments at ELN milestones on first and second TKI are described in **Table III**.

First-line TKI therapy

Median follow-up duration on first-line TKI and molecular responses to first-line TKI therapy are shown in **Table IV**. Time to discontinuation of first TKI for patients on imatinib vs 2G-TKI is shown in **Fig 1**. For patients receiving imatinib or nilotinib, respective median starting doses were 400 or 600 mg/day; 24/203 (12%) and 8/50 (16%) had dose reductions, while 14% and 12% had dose interruptions.

Quantifiable molecular or cytogenetic assessments were performed at ≥1 ELN milestone during first-line TKI in 223 patients (87%) (**Fig 2**). Forty-eight patients had ≥1 failure; 11 (23%) remained on first-line TKI (median follow-up, 13.8 months [interquartile range (IQR), 12.8-25.9]), and 37 (77%) switched TKIs (median follow-up, 25.1 months [IQR, 14.3-32.6]).

Second-line TKI therapy

At least one TKI switch occurred in 113 patients (44%); 54 (21%) switched more than once. Reasons for the first switch were resistance in 73 (65%), intolerance in 38 (34%) and other reasons in 2 (2%) (**Supplementary Table III**). Thirteen patients (12%) switched to imatinib, 68 (60%) to nilotinib, 20 (18%) to dasatinib, 11 (10%) to bosutinib and one (1%) to ponatinib (**Supplementary Table IV)**. For patients receiving second-line imatinib, nilotinib, dasatinib and bosutinib, median starting doses (range) were 400 (200-400), 600 (200-800), 100 (50-100) and 300 (100-500) mg/day, respectively.

Median follow-up duration after switching to second TKI was 23.7 months (range, 1.2-54.1) (**Table V**). MMR at any time and DMR at any time were observed in 37/51 (73%) and 21/51 (41%) patients with ≥13 months' follow-up on second line. Molecular responses to second-line TKI for all patients regardless of follow-up duration are shown in **Supplementary Table V**.

Of 113 patients who switched TKI at least once, 18 (16%) had failure on second-line TKI (**Supplementary Fig 1**); 7 (39%) remained on that TKI (median follow-up, 24.3 months [IQR, 11.6-31.0]), while 11 (61%) switched again (median follow-up, 27.5 months [IQR, 16.4-33.8]).

Kinase domain mutation analysis

BCR-ABL1 kinase domain mutational analysis was performed prior to the first switch in 24 patients (21%), including 20 (27%) who switched due to resistance and 4 (10%) who switched due to intolerance or other reasons. Clinically actionable mutations were identified in 6 patients (**Supplementary Table VI).**

Overall TKI pathways

Among all patients, 144 (56%) received only a first-line TKI, and 59 (23%), 35 (14%), 16 (6%) and 3 (1%) received 2, 3, 4 and 5 TKIs, respectively; sequences of TKI received are described in **Supplementary Table IV**. Eleven patients received the same TKI in multiple lines of therapy.

Disease progression

Ten patients progressed to AP and/or BP, and 15 patients died (10 in CP and 5 after progression). Survival outcomes and treatments to manage progression are summarized in **Fig 3**.

Discussion

The management of CML has undergone dramatic changes; however, it remains unclear whether real-world practice in the UK has evolved with these developments. We conducted the UK TARGET CML study to assess this question, with a particular focus on (1) TKI treatment pathways, (2) implementation of ELN recommendations for molecular-based patient management, (3) attainment of DMR with first- and second-line TKI in real-world practice and (4) assessment of baseline CV risk factors.

Despite relatively short median follow-up (<33 months), almost half of patients switched from first-line TKI, most often due to resistance (65%). In addition, 21% of patients received ≥3 lines of TKIs. This frequency of TKI switching was somewhat higher than that observed in prospective clinical trials, such as the pivotal trial of frontline imatinib (International Randomized Study of Interferon and STI571 [IRIS]), which reported that 34% of patients discontinued treatment after 6 years of follow-up, although no other alternative TKI was available at the time of IRIS recruitment (Hochhaus *et al*, 2009). In IRIS long-term follow-up (median, 10.9 years), imatinib discontinuation was most frequently attributed to unsatisfactory therapeutic effect (15.9%), withdrawal of consent (10.3%), or AEs (6.9%) (Hochhaus *et al*, 2017a). Similarly, in the frontline trial of nilotinib (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients [ENESTnd]), treatment discontinuations were most frequently due to suboptimal response/treatment failure or AEs/abnormal laboratory values (12% each by the 5-year data cutoff among patients allocated to nilotinib 300 mg twice daily) (Hochhaus *et al*, 2016). We found that in real-world practice, approximately half of patients required a change of TKI, highlighting the importance of optimal monitoring of molecular responses and treatment-related side effects to ensure proper use of TKIs and timely switching. These data also demonstrated the ongoing challenge of establishing a satisfactory, long-term treatment, with multiple TKI switches being common.

Although 58% of patients had a recorded comorbidity, patients generally had poorly documented baseline clinical characteristics and prognostic scores. Demographic and baseline characteristics were not dissimilar from those of other real-world cohorts (Goldberg *et al*, 2017; Hoglund *et al*, 2013; Nesr *et al*, 2018), although prognostic scores were better documented (98%) in the

Swedish CML registry (Hoglund *et al*, 2013). CV events have been reported to be increased with 2G-TKIs (Chai-Adisaksopha *et al*, 2016; Cortes *et al*, 2016; Hochhaus *et al*, 2016), and CV risk factors should therefore be carefully considered when choosing a TKI. Even with first-line imatinib, it is important to assess CV risk given that approximately half of patients will require a switch to a 2G-TKI at some point. Although late complications with 2G-TKIs were not fully understood or evaluable at the time of ELN 2013, the guidelines nevertheless recommended continued clinical monitoring of all patients. Several CV risk factors were very poorly documented in our cohort, and any use of validated CV risk tools, such as QRISK2, was rarely documented. Baseline blood pressure was documented in fewer than one-third of patients; when baseline blood pressure was recorded, it was often elevated, with 3 patients in hypertensive crisis, illustrating the importance of documenting this parameter so that hypertension can be managed appropriately. However, some evidence was observed that CV comorbidities at baseline played a role in first-line TKI choice, with patients appearing more likely to receive first-line imatinib if a CV comorbidity was documented.

Currently, the UK National Institute for Health and Care Excellence (NICE) recommends NHS funding in England of imatinib, nilotinib or dasatinib in the first line and nilotinib, dasatinib, bosutinib or ponatinib in later lines (NICE, 2018). In this cohort, first-line treatment was mostly imatinib or nilotinib (<2% received first-line dasatinib), and second-line treatment was mostly nilotinib, reflecting NICE recommendations at the start of treatment for these patients (dasatinib was not routinely available). Patients were more likely to receive first-line 2G-TKIs than imatinib if they were younger and had no documented comorbidities. Overall, prognostic scores were poorly documented despite strong evidence that these risk scores remain highly predictive

of disease response in the TKI era (Hochhaus *et al*, 2016). We did not find evidence that prognostic scores played a major role in first-line TKI choice, with a majority of patients identified as high risk by Sokal, EUTOS or Hasford criteria being treated with imatinib. Overall, 4% of patients progressed to AP and/or BP, corresponding well with the results of the Swedish CML registry (3% by 12 months) (Hoglund *et al*, 2013).

One key finding of this study is that ELN 2013 monitoring recommendations were not consistently implemented. Patients frequently did not have assessments at recommended time points. This finding is consistent with those from the SIMPLICITY study, which reported that monitoring was conducted less frequently than recommended, although with higher frequency in Europe than the United States (Goldberg *et al*, 2017). This finding is important because a previous study showed that patients without frequent molecular monitoring were at higher risk of disease progression (Goldberg *et al*, 2013). In addition, frequent molecular monitoring (3-4 times per year) was associated with greater TKI treatment adherence in patients with CML (Guerin *et al*, 2014).

Overall, in our study, 86% of patients had ≥3 molecular response tests during their first year of TKI treatment, while SIMPLICITY reported 46% for Europe (Goldberg *et al*, 2017), a finding that potentially reflects UK-specific practice or changes in practice over time (UK patients who were first treated in 2013-2017 were compared with SIMPLICITY patients first treated in 2010-2015). Furthermore, our UK study observed a relatively high level of testing for early molecular response (EMR) at 3 months (81%) compared with SIMPLICITY (32%), indicating rapid adoption of molecular monitoring at early milestones in the UK (Goldberg *et al*, 2017).

However, despite a generous 1-month window applied around ELN milestones, a large proportion of patients (≈20%-30%) were still without evaluable molecular or cytogenetic test results at any given time point during their first year of TKI treatment. Moreover, 13% of patients had no evaluable molecular or cytogenetic result at any ELN milestone during the first year of TKI treatment.

ELN recommended that a patient with ELN-defined failure should have their TKI switched to reduce the risk of progression. Nevertheless, a number of patients in TARGET remained on first-line TKI despite ELN-defined treatment failure.

Strikingly, *BCR-ABL1* kinase domain mutational analyses, recommended by ELN in warning or failure, were infrequently performed, even in patients with documented resistance, despite the known importance of mutation status for subsequent TKI selection. Patients did not always have recommended baseline assessments such as qualitative PCR despite its importance in determining *BCR-ABL1* transcript type, which can affect future molecular monitoring, especially at the low levels before consideration for TFR. Furthermore, although bone marrow and cytogenetic analysis still have an essential role in assessment of patients at baseline, many patients were managed without bone marrow or cytogenetic analysis. Bone marrow evaluation before TKI switching was infrequently performed, which may reflect the current use of PCR thresholds for interpretation of resistance.

Clinical trials have shown that 2G-TKIs lead to improved rates of molecular responses compared with imatinib (Cortes *et al*, 2018a; Cortes *et al*, 2016; Hochhaus *et al*, 2016). In this cohort, observed rates of EMR and MMR at ELN milestones and DMR at any time during first-line TKI were higher with 2G-TKIs than with imatinib, confirming the results in this real-world setting. While EMR and MMR were defined as optimal responses in ELN 2013 (Baccarani *et al*, 2013), treatment goals are evolving to include deeper responses and TFR (Hochhaus *et al*, 2017b; NCCN, 2020; Rea *et al*, 2018). Studies have shown that deeper molecular responses were associated with improved outcomes compared with complete cytogenetic response (Etienne *et al*, 2014; Hehlmann *et al*, 2014), and a sustained DMR is a prerequisite for attempting TFR in both clinical practice guidelines (Hochhaus *et al*, 2017b; NCCN, 2020; Rea *et al*, 2018) and clinical trials (Mahon *et al*, 2018; Ross *et al*, 2018). Clinical studies have demonstrated that 2G-TKIs can also lead to improved rates of DMR in the second line (Hughes *et al*, 2017). Results from our study showed that patients switching from first-line treatment may achieve not only optimal responses but also deeper responses, including patients with prior resistance or ELN-defined failure.

A criticism of observational studies is the increased risk of selection bias and confounding, precluding the robust analysis and conclusions provided by randomized controlled trials. However, real-world evidence plays an important role in allowing physicians to reflect on current practice. Our study demonstrated that almost half of patients required TKI switch in real-world practice and that optimal and deep responses can be achieved by patients who switch. However, inadequate CV risk assessment, response monitoring, and mutational analysis increased the risk of inappropriate patient management and, as such, the findings of this study

highlighted key areas for improvement in care for patients with CML. Further consideration for improving implementation of guidelines in real-world clinical practice, including very recent updates to the ELN recommendations (Hochhaus *et al* 2020), is warranted.

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Author contributions

AJM and DM designed the research study, performed the research, analysed the data and wrote the paper. REC and PN designed the research study, performed the research and analysed the data. JR and FG designed the research study, analysed the data and wrote the paper. NCPC, LF and SJC designed the research and analysed the data. FWa, JB, FLD, SA, MD, JT, MFM, GC, BH, FWi, MS, MR and SM performed the research and analysed the data.

Competing interests

AJM participated in advisory boards for Novartis, Bristol-Myers Squibb (BMS) and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis. REC participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis, BMS and Pfizer. NCPC participated in advisory boards for Novartis, BMS and Pfizer; received honoraria from Novartis, BMS, Pfizer and Ariad/Incyte; and received research funding from Novartis, BMS and Pfizer. FLD received honoraria, travel, accommodations and expenses from Novartis and Pfizer. MFM participated in advisory boards for Novartis and received honoraria from Novartis, Pfizer and BMS. SM participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis. FWa received educational grants from Pfizer and Novartis. MR participated in advisory boards and received honoraria from Novartis. JB participated in advisory boards and received honoraria from Novartis, Pfizer and Incyte. SA participated in advisory boards and received honorarium, travel and accommodations from Novartis. MD received honoraria from Novartis and Pfizer and research funding from Novartis. JT received support for conference attendance from Novartis. BH participated in advisory boards for Novartis, Pfizer and BMS. FWi received honoraria, travel, accommodation and expenses from Novartis. DM received honoraria from Incyte, Novartis, Pfizer and BMS. JR and SJC are employees and shareholders of Novartis. LF is a former employee and shareholder of Novartis. FG is an employee of OPEN VIE contracted by Novartis. PN, MS and GC declared no conflict of interest.

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548 **Table I. Patient demographics and baseline characteristics**

	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)	First-line nilotinib (n=50)
Sex, n (%)				
Male	144 (56)	119 (59)	25 (46)	24 (48)
Female	113 (44)	84 (41)	29 (54)	26 (52)
Age at initiation of first-line TKI, median (range [IQR]), years	53.5 (18.4-92.4 [38.8-65.8])	55.4 (18.4-92.4 [39.9-67.4])	45.8 (20.3-79.5 [36.4-59.6])	45.1 (20.3-79.5 [36.1-59.6])
Time from CML diagnosis to start of first TKI, median (IQR), days	7.0 (1.0-20.0)	8.0 (2.0-20.3)	6.0 (1.0-11.0)	6.0 (1.0-11.0)
Assessments prior to first-line TKI, n (%)				
RQ-PCR	169 (66)	140 (69)	29 (54)	26 (52)
Qualitative PCR (b2a2, b3a2, other)	140 (54)	107 (53)	33 (61)	30 (60)
CBA	180 (70)	146 (72)	34 (63)	31 (62)
FISH	155 (60)	117 (58)	38 (70)	34 (68)
CBA or FISH (bone marrow)	154 (60)	119 (59)	35 (65)	32 (64)
CBA or FISH (peripheral blood)	54 (21)	45 (22)	9 (17)	9 (18)
Both CBA/FISH and RQ-PCR	139 (54)	117 (58)	22 (41)	20 (40)
Treatment for CML prior to first-line TKI, n (%)				
Yes	126 (49)	97 (48)	29 (54)	26 (52)
Prior treatment[a,b]				
Hydroxycarbamide	116 (92)	89 (92)	27 (93)	24 (92)
Leukapheresis	2 (2)	2 (2)	0	0
Anagrelide	1 (1)	1 (1)	0	0
Interferon	1 (1)	1 (1)	0	0
Aspirin	1 (1)	0	1 (3)	1 (4)
No	128 (50)	104 (51)	24 (44)	23 (46)
Unknown	3 (1)	2 (1)	1 (2)	1 (2)
Ph chromosome at baseline				
Yes	212 (82)	175 (86)	37 (69)	35 (70)
No	3 (1)	1 (<1)	2 (4)	2 (4)
Unknown	42 (16)	27 (13)	15 (28)	13 (26)
Clinical characteristics				
WBC count, median (IQR), 10^9/l	82.4 (31.2-177.3)	77.0 (31.2-158.0)	92.9 (32.3-201.4)	92.1 (32.5-198.9)
Unknown, n (%)[c]	4 (2)	1 (<1)	3 (6)	2 (4)
Platelet count, median (IQR), 10^9/l	404.0 (252.5-603.0)	393.5 (244.8-603.0)	439.0 (339.0-578.0)	441.0 (342.8-589.3)
Unknown, n (%)[c]	14 (5)	11 (5)	3 (6)	2 (4)
Basophils, median (IQR), %	3.9 (2.0-7.0)	3.3 (2.0-6.0)	5.0 (2.3-8.0)	4.0 (2.3-8.3)
Unknown, n (%)[c]	59 (23)	46 (23)	13 (24)	13 (26)
Eosinophils, median (IQR), %	2.0 (1.1-3.7)	2.0 (1.1-3.5)	2.0 (1.3-3.7)	2.0 (1.3-3.0)
Unknown, n (%)[c]	58 (23)	45 (22)	13 (24)	13 (26)
Blasts, median (IQR) (%)	2.0 (1.0-4.8)	2.0 (1.0-3.4)	3.0 (1.6-8.4)	3.0 (1.5-6.0)
Unknown, n (%)[c]	101 (39)	77 (38)	24 (44)	23 (46)
Spleen size below costal margin, median (IQR), cm[d]	1.3 (0.0-10.1)	1.0 (0.0-10.1)	4.0 (0.0-10.3)	2.0 (0.0-10.0)
Unknown, n (%)[c]	85 (33)	67 (33)	18 (33)	17 (34)
Sokal risk score, n (%)[e]				
Low risk	52 (20)	43 (21)	9 (17)	8 (16)
Intermediate risk	54 (21)	41 (20)	13 (24)	13 (26)
High risk	42 (16)	31 (15)	11 (20)	9 (18)

No score recorded and required components not all recorded	109 (42)	88 (43)	21 (39)	20 (40)
EUTOS score, n (%)[f]				
Low risk	110 (43)	90 (44)	20 (37)	19 (38)
High risk	34 (13)	23 (11)	11 (20)	9 (18)
No score recorded and required components not all recorded[g]	113 (44)	90 (44)	23 (43)	22 (44)
Hasford score, n (%)[h]				
Low risk	25 (10)	19 (9)	6 (11)	5 (10)
Intermediate risk	35 (14)	32 (16)	3 (6)	3 (6)
High risk	19 (7)	13 (6)	6 (11)	4 (8)
No score recorded and required components not all recorded	178 (69)	139 (68)	39 (72)	38 (76)
Comorbidities, n (%)				
None recorded	108 (42)	80 (39)	28 (52)	26 (52)
≥1 recorded[i,j]	149 (58)	123 (61)	26 (48)	24 (48)
CV comorbidities	81 (32)	74 (36)	7 (13)	6 (12)
Diabetes	25 (10)	21 (10)	4 (7)	4 (8)
Respiratory disease	20 (8)	17 (8)	3 (6)	3 (6)
Renal disease	16 (6)	14 (7)	2 (4)	2 (4)
Non-haematological cancer	9 (4)	8 (4)	1 (2)	1 (2)
Hepatic disease	4 (2)	3 (1)	1 (2)	1 (2)
Other	86 (33)	70 (34)	16 (30)	15 (30)

2G-TKI, second-generation tyrosine kinase inhibitor; CBA, chromosome banding analysis; CML, chronic myeloid leukaemia; CV, cardiovascular; EUTOS, European Treatment and Outcomes Study; FISH, fluorescence in situ hybridization; IQR, interquartile range; Ph, Philadelphia chromosome; RQ-PCR, real-time quantitative polymerase chain reaction; WBC, white blood cell.

[a] Patients may have received multiple prior treatments.

[b] Proportion of patients with each prior treatment was calculated out of the total number of patients who received prior treatment.

[c] Proportion of patients with unknown clinical characteristics was calculated out of the total number of patients in each column.

[d] Spleens reported to be "normal" or "nonpalpable" were considered to be 0 cm below the costal margin.

[e] Among 148 patients who received any first-line TKI and had an available Sokal risk score at diagnosis, the score was documented for 96 (65%) and not documented and instead calculated during this analysis for 52 (35%).

[f] Among 144 patients who received any first-line TKI and had an available EUTOS risk score at diagnosis, the score was documented for 36 (25%) and not documented and instead calculated during this analysis for 108 (75%).

[g] Includes patients who had a risk category recorded but no score recorded.

[h] Hasford scores were not collected in case report forms and were calculated if required data were available.

[i] Patients may have had multiple comorbidities.

[j] Proportion of patients with each comorbidity was calculated out of the total number of patients in each column.

Table II. Baseline CV comorbidities and risk factors

n (%)	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)	First-line nilotinib (n=50)
Diabetes	25 (10)	21 (10)	4 (7)	4 (8)
Smoking				
Documented[a]	174 (68)	140 (69)	34 (63)	32 (64)
Current smoker	38 (22)	35 (25)	3 (9)	3 (9)
Ex-smoker	46 (26)	39 (28)	7 (21)	6 (19)
Never smoked	88 (51)	65 (46)	23 (68)	22 (69)
Unclear	2 (1)[b]	1 (1)[b]	1 (3)[b]	1 (3)[b]
BMI >30 documented	16 (6)	14 (7)	2 (4)	2 (4)
CV comorbidities				
None recorded	176 (68)	129 (64)	47 (87)	44 (88)
≥1 recorded[c,d]	81 (32)	74 (36)	7 (13)	6 (12)
Hypertension	58 (23)	52 (26)	6 (11)	5 (10)
Hyperlipidaemia	28 (11)	26 (13)	2 (4)	2 (4)
Coronary artery disease	14 (5)	12 (6)	2 (4)	2 (4)
Myocardial infarction	11 (4)	10 (5)	1 (2)	1 (2)
Coronary artery bypass graft	9 (4)	8 (4)	1 (2)	1 (2)
Arrhythmias	8 (3)	7 (3)	1 (2)	1 (2)
Cerebrovascular accident	4 (2)	4 (2)	0	0
Transient ischemic attack	4 (2)	3 (1)	1 (2)	1 (2)
Congestive heart failure	3 (1)	2 (1)	1 (2)	1 (2)
Unstable angina	2 (1)	2 (1)	0	0
Percutaneous coronary intervention	2 (1)	2 (1)	0	0
Peripheral vascular disease	2 (1)	2 (1)	0	0
History of CV disease				
Not documented	101 (39)	80 (39)	21 (39)	20 (40)
Documentation unknown[e]	1 (<1)	1 (<1)	0	0
Documented[f]	155 (60)	122 (60)	33 (61)	30 (60)
No history	26 (17)	23 (19)	3 (9)	3 (10)
Details of history not provided	104 (67)	76 (62)	28 (85)	25 (83)
Details of history provided	25 (16)	23 (19)	2 (6)	2 (7)
Family history of CV disease				
Not documented	159 (62)	128 (63)	31 (57)	29 (58)
Documentation unknown[e]	1 (<1)	1 (<1)	0	0
Documented	97 (38)	74 (36)	23 (43)	21 (42)

2G-TKI, second-generation tyrosine kinase inhibitor; BMI, body mass index; CV, cardiovascular.

[a] Proportion of patients in each smoking category was calculated based on the number of patients with documented smoking status.

[b] Two patients were recorded as "does not smoke"; it was unclear whether they were ex-smokers or never smoked.

[c] Patients could be listed as having >1 CV comorbidity.

[d] Proportion of patients with CV comorbidities was calculated based on total number of patients in each column.

[e] One patient was transferred from another hospital prior to TKI treatment; it was unclear if this patient's personal or family history of vascular disease had been documented prior to TKI treatment.

[f] Proportion of patients within each category was calculated based on the number of patients who had documented CV disease history.

Table III. Frequency of molecular and cytogenetic assessments at ELN milestones for patients on first and second TKI

	All patients n (%)	Imatinib first line n (%)	Second-generation first line n (%)	Nilotinib first line n (%)
First TKI				
RQ-PCR				
3 months[a]	180/223 (81)	143/173 (83)	37/50 (74)	35/47 (74)
6 months[b]	141/199 (71)	105/154 (68)	36/45 (80)	34/42 (81)
12 months[c]	117/170 (69)	95/132 (72)	22/38 (58)	21/35 (60)
CBA/FISH				
3 months[a]	15/223 (7)	15/173 (9)	0/50 (0)	0/47 (0)
6 months[b]	9/199 (5)	8/154 (5)	1/45 (2)	1/42 (2)
12 months[c]	2/170 (1)	2/132 (2)	0/38 (0)	0/35 (0)
CBA/FISH and/or RQ-PCR				
3 months[a]	186/223 (83)	148/173 (86)	38/50 (76)	36/47 (77)
6 months[b]	151/199 (76)	114/154 (74)	37/45 (82)	35/42 (83)
12 months[c]	117/170 (69)	95/132 (72)	22/38 (58)	21/35 (60)
Second TKI				
RQ-PCR				
3 months[a]	63/82 (77)	8/10 (80)	55/72 (76)	43/54 (80)
6 months[b]	44/66 (67)	4/8 (50)	40/58 (69)	31/46 (67)
12 months[c]	27/52 (52)	4/8 (50)	23/44 (52)	19/39 (49)
CBA or FISH				
3 months[a]	12/82 (15)	2/10 (20)	10/72 (14)	9/54 (17)
6 months[b]	4/66 (6)	0/8 (0)	4/58 (7)	4/46 (9)
12 months[c]	1/52 (2)	0/8 (0)	1/44 (2)	1/39 (3)
CBA/FISH and/or RQ-PCR				
3 months[a]	65/82 (79)	8/10 (80)	57/72 (79)	45/54 (83)
6 months[b]	45/66 (68)	4/8 (50)	41/58 (71)	32/46 (70)
12 months[c]	27/52 (52)	4/8 (50)	23/44 (52)	19/39 (49)
≥1 assessment at an ELN milestone (first- or second-line TKI)[a]	239/257 (93)	189/203 (93)	50/54 (93)	48/50 (96)

CBA, chromosome banding analysis; ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; RQ-PCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

[a] Denominator included patients with ≥4 months' follow-up on that TKI.

[b] Denominator included patients with ≥7 months' follow-up on that TKI.

[c] Denominator included patients with ≥13 months' follow-up on that TKI.

Table IV. Summary of molecular responses to first-line TKI therapy[a]

	Overall responses			First-line TKI			
	First-line imatinib (n=203)	First-line 2G-TKI (n=54)[b]	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)[b]	First-line nilotinib (n=50)	All patients (N=257)
Median follow-up duration[c] on each TKI (range), months	33.3 (12.6-58.6)	30.0 (13.2-56.8)	32.9 (12.6-58.6)	16.7 (0.5-54.8)	20.8 (0.5-55.3)	21.3 (0.5-55.3)	17.5 (0.5-55.3)
EMR at 3 months (±1 month), in patients with 3-month molecular response assessments, n (%)	88/163 (54)	29/41 (71)	117/204 (57)	88/156 (56)	28/38 (74)	26/36 (72)	116/194 (60)
MMR by 12 months (±1 month), n (%)	84 (41)	28 (52)	112 (44)	71 (35)	26 (48)	25 (50)	97 (38)
MMR at any time, n (%)	156 (77)	42 (78)	198 (77)	102 (50)	34 (63)	32 (64)	136 (53)
DMR at any time, n (%)	95 (47)	35 (65)	130 (51)	58 (29)	29 (54)	27 (54)	87 (34)

2G-TKI, second-generation tyrosine kinase inhibitor; DMR, deep molecular response; EMR, early molecular response; IS, International Scale; MMR, major molecular response.

[a] Patients could appear in multiple molecular response categories. Molecular responses were assessed as EMR (*BCR-ABL1*^{IS} ≤10% at 3 months), MMR (*BCR-ABL1*^{IS} ≤0.1%) by 12 months, MMR at any time and DMR (*BCR-ABL1*^{IS} ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used.

[b] Fifty patients received first-line nilotinib, and 4 received first-line dasatinib.

[c] The columns for overall response reported the duration of follow-up for all TKI therapies, including later-line TKIs in patients who switched from their first-line TKI (from start of first-line TKI to most recent data collection, akin to an intention-to-treat analysis). The columns for first-line TKI therapy reported the duration of follow-up for only first-line TKI therapy (from start of first-line TKI to most recent data collection or death in patients who continued receiving first-line TKI or to end of first-line TKI for patients who switched to a second-line TKI).

Table V. Summary of molecular responses after switching to second-line TKI therapy[a]

	All switched patients (n=113)	Second-line imatinib (n=13)	Second-line 2G-TKI (n=100)[b]	Second-line nilotinib (n=68)	Switched to second line for resistance (n=73)	Switched to second line for intolerance or other reason (n=40)[c]
Median follow-up post first switch (range), months[d]	23.7 (1.2-54.1)	22.5 (4.9-43.0)	23.9 (1.2-54.1)	29.7 (1.2-52.4)	27.4 (1.2-51.4)	20.1 (2.8-54.1)
Median follow-up on second-line TKI (range), months[e]	23.9 (13.6-50.2)	19.2 (13.6-43.0)	28.6 (13.9-50.2)	27.3 (13.9-50.2)	25.6 (13.9-46.5)	20.3 (13.6-50.2)
EMR at 3 months (±1 month) on second TKI in patients with 3-month molecular response assessments, n (%)[f]	59/70 (84)	10/10 (100)	49/60 (82)	38/45 (84)	39/47 (83)	20/23 (87)
MMR by 12 months (±1 month) on second TKI, n (%)[g]	30/50 (60)	4/7 (57)	26/43 (60)	24/38 (63)	21/35 (60)	9/15 (60)
MMR at any time on second TKI, n (%)[g]	37/51 (73)	4/8 (50)	33/43 (77)	29/38 (76)	27/36 (75)	10/15 (67)
DMR at any time on second TKI, n (%)[g]	21/51 (41)	2/8 (25)	19/43 (44)	17/38 (45)	15/36 (42)	6/15 (40)

2G-TKI, second-generation tyrosine kinase inhibitor; DMR, deep molecular response; EMR, early molecular response; IS, International Scale; MMR, major molecular response.

[a] Patients could appear in multiple molecular response categories. Molecular responses after switch to second TKI were assessed as EMR (*BCR-ABL1*^{IS} ≤10% at 3 months), MMR (*BCR-ABL1*^{IS} ≤0.1%) by 12 months, MMR at any time and DMR (*BCR-ABL1*^{IS} ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used.

[b] Switched to 2G-TKI (n=68 nilotinib, n=20 dasatinib, n=11 bosutinib, n=1 ponatinib).

[c] Switched for intolerance (n=38) or switched for another reason (n=2).

[d] Duration from start of second-line TKI to last data collection or death (included patients with ≥1 switch).

[e] Duration from start of second-line TKI to last data collection, date of switch to a third-line TKI, or death.

[f] EMR defined as *BCR-ABL1*^{IS} ≤10% at 3 months (±1 month); only those patients with *BCR-ABL1* available at 3 months were included.

[g] MMR (≤0.1% *BCR-ABL1*); DMR (≤0.01% *BCR-ABL1*); only those patients with ≥13 months' follow-up were included.

Fig 1. Kaplan-Meier curve: time to discontinuation of first-line TKI

Patients who had not switched from first TKI at point of data collection were censored at date of data collection or death. Months on first TKI were unknown for 10 patients on imatinib. TKI, tyrosine kinase inhibitor.

Fig 2. TKI treatment pathways and molecular responses for patients with ELN optimal, warning (at single vs multiple ELN milestones) or failure responses while on first-line TKI

[a] To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points (3, 6 and 12 months). In patients with multiple test results available, any patient with a failure response to first-line TKI at an ELN milestone (regardless of other responses achieved at earlier milestones) was classified as having a failure response. Patients in the optimal category had only optimal responses at an ELN milestone (3, 6 or 12 months) with either molecular or cytogenetic assessment (where a molecular test was not available). Patients in the warning category had a warning at any milestone with either assessment but had no failure at any milestone with either assessment. Patients without assessments at any ELN milestone could not be categorized. Thirty-four patients had no evaluable test at any ELN milestone by either molecular or cytogenetic test.

[b] Response may have been observed at any time. Duration of follow up varied; patient may have had ≥1 subsequent TKI switch. Forty-eight patients had ≥1 failure; 11 (23%) remained on first-line TKI (median follow-up, 13.8 months [IQR, 12.8-25.9 months]), and 37 (77%) switched TKIs (median follow-up, 25.1 months [IQR, 14.3-32.6 months]). Of those who switched, 22 had their first failure at 6 months (*BCR-ABL1*^{IS} range, 10.1%-60.1%; 2 patients had a failure according to FISH), and 15 had their first failure at 12 months (*BCR-ABL1*^{IS} range, 1.2%-12.7%). Among these patients with a failure who switched TKIs, 17 (46%) and 10 (27%) achieved MMR and DMR at any time, respectively, vs 4 (36%) and 0 patients who did not switch TKIs. Of 81 patients with warning but no failure, 52 (64%) remained on first-line TKI (median follow-up 28.4 months [IQR, 13.7-40.4 months]), and 29 (36%) switched TKIs (median follow-up 30.9 months [IQR, 20.3-38.3 months]). Of those who switched TKIs, 19/29 had ≥1 additional RQ-PCR assessment between the initial warning and TKI switch. Of 34 patients without any quantifiable assessment at any ELN milestone, 27 (79%) switched TKIs.

[c] Of 48 patients with ELN-defined failure responses, 39 were treated with imatinib as first-line therapy and 9 with a 2G-TKI; 38 patients (79%) also had an ELN-defined warning at a prior ELN time point (with either a molecular or cytogenetic test).

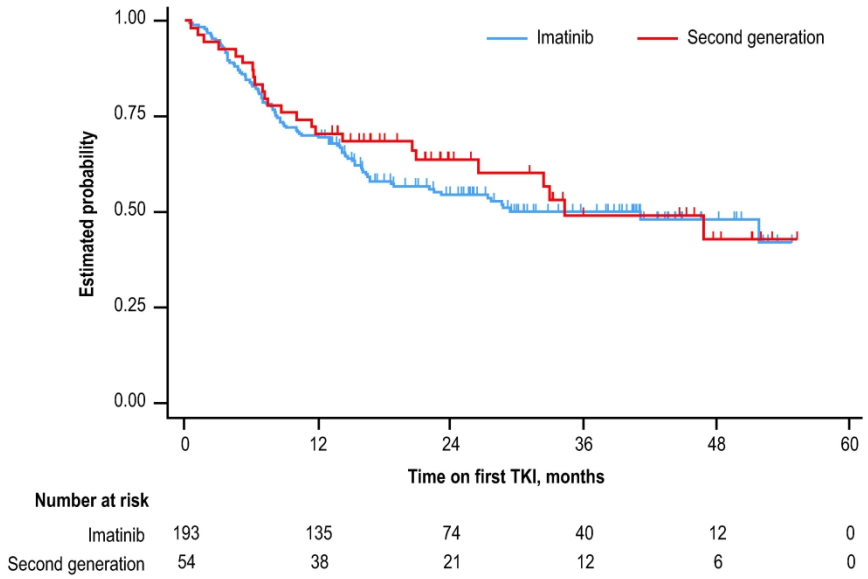
DMR, deep molecular response; ELN, European LeukemiaNet; EMR, early molecular response; FISH, fluorescence in situ hybridization; IQR, interquartile range; IS, International Scale; MMR, major molecular response; RQ-PCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

Fig 3. Disease progression[a]

[a] Eight patients (7 on imatinib, 1 on a second-generation TKI) progressed to accelerated phase (AP) during the course of the study. The median time to progression was 16.5 months (range, 2.1-31.1; IQR, 7.5-26.4; time to progression was unknown for one patient on first-line imatinib). Three patients had a prior warning response at an ELN milestone (all 3 patients received imatinib as first TKI), and 3 patients had a failure response at an ELN milestone (2 patients received imatinib first line and 1 patient received nilotinib). The other 2 patients who progressed to AP had no prior evaluable response at an ELN milestone (both patients received first-line imatinib). Treatments for progression to AP were TKIs in 3 patients, chemotherapy in 4 patients and allogenic haematopoietic stem cell transplant (HSCT) in 5 patients. Six patients progressed to BP (all received first-line imatinib), including 4 who were previously recorded as progressing to AP. Median time from start of first-line TKI to progression to BP was 22.7 months (range 1.2- 32.1; IQR, 17.2-30.1). Treatments for progression to BP were TKIs in 4 patients, chemotherapy in 4 patients, allogenic HSCT in 2 patients and haploidentical allogenic HSCT in one patient. Among 4 patients who progressed to AP only, 2 received 1 TKI prior to progression, 1 received 3 TKIs prior to progression, and 1 had an unknown date of disease progression. Among 4 patients who progressed to AP and BP, 2 each received 1 or 2 TKIs prior to their earliest progression, respectively. Among 2 patients who progressed to BP only, 1 each received 1 or 2 TKIs prior to progression, respectively. None of the patients who progressed were observed to have only ELN-optimal responses to first-line TKI; 3 patients had ≥1 failure, 4 had ≥1 warning and 2 had no available assessments at ELN milestones. In the 10 patients who progressed to AP and/or BP, baseline Sokal score was recorded as high for 4, intermediate for 2, low for 1 and unknown for 3.

[b] A total of 15/257 patients died during the study observation period; 5 of these patients had progressed to AP and/or BP prior to death (n=4 had blast crisis prior to death). Another 5 patients had progressed but were still alive at data collection (n=2 had blast crisis); all had received alternative treatment with 4 of 5 receiving both transplant and chemotherapy after progressing (n=1 after alternative TKI); the other patient received a transplant only.

AP, accelerated phase; BP, blast phase; ELN, European LeukemiaNet; TKI, tyrosine kinase inhibitor.



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Patients who had not switched from first TKI at point of data collection were censored at date of data collection or death. Months on first TKI were unknown for 10 patients on imatinib. TKI, tyrosine kinase inhibitor.

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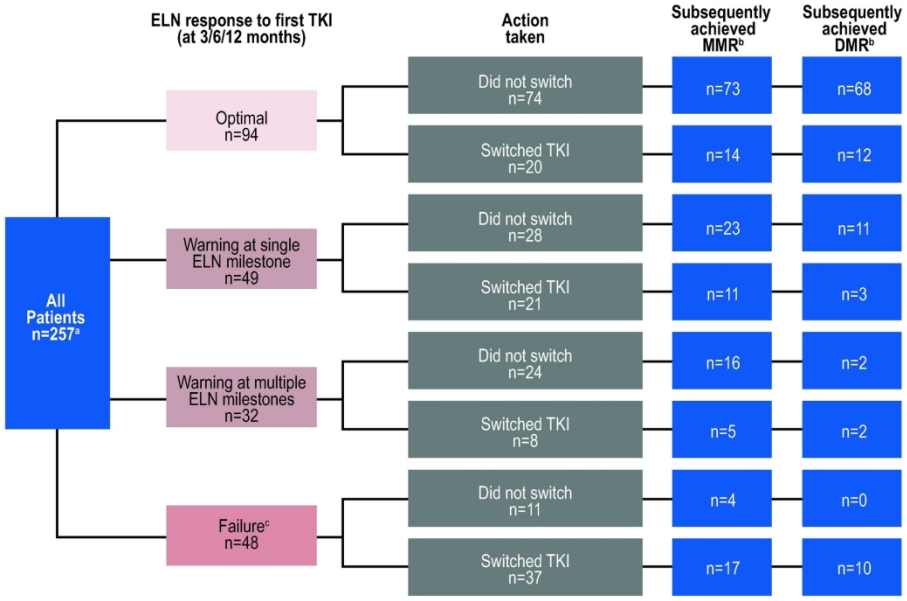

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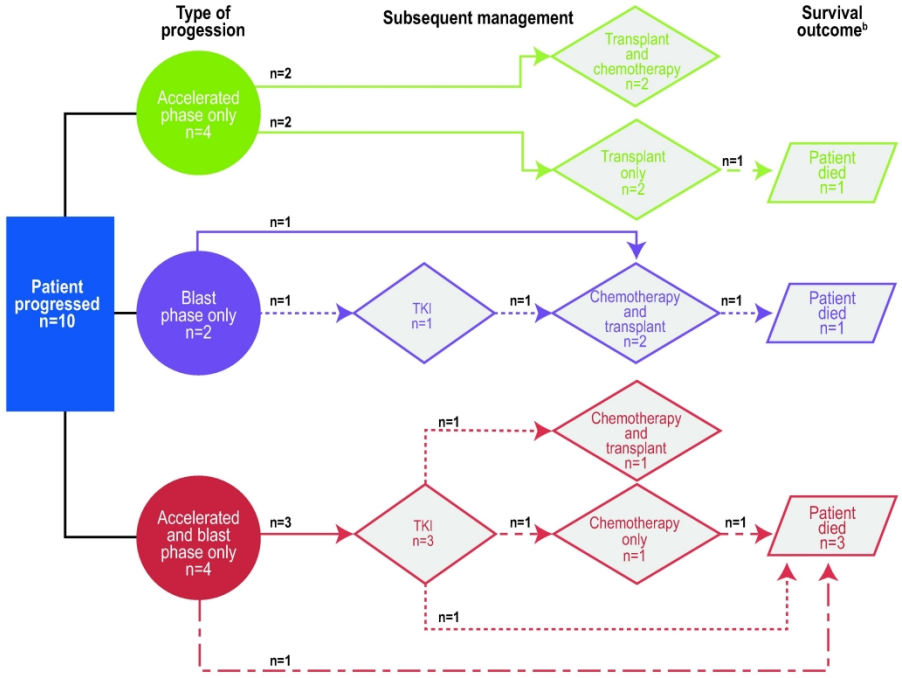

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Real-world tyrosine kinase inhibitor treatment pathways, monitoring patterns and responses in patients with chronic myeloid leukaemia in the United Kingdom: the UK TARGET CML study

Running title: Tyrosine kinase inhibitor use in the real world

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Abstract: 200 (unstructured; word limit: 200)

Current Word count: 30562997 (limit excluding abstract, tables/figures and references: 3000)

Tables/figures: 8 (limit: 8 total)

References: 310 (limit: 60)

Abstract

Management of chronic myeloid leukaemia (CML) has recently undergone dramatic changes, prompting the European LeukemiaNet (ELN) to issue recommendations in 2013; however, it remains unclear whether real-world CML management is consistent with these goals. We report results of UK TARGET CML, a retrospective observational study of 257 patients with chronic-phase CML prescribed a first-line TKI between 2013 and 2017, most of whom received first-line imatinib (n=203). Although 44% of patients required ≥1 change of TKI, these real-world data revealed that molecular assessments were frequently missed, 23% of patients with ELN-defined treatment failure did not switch TKI and kinase domain mutation analysis was performed in only 49% of patients who switched TKI for resistance. Major molecular response (MMR; *BCR-ABL1*^{IS} ≤0.1%) and deep molecular response (DMR; *BCR-ABL1*^{IS} ≤0.01%) were observed in 50% and 29%, respectively, of patients treated with first-line imatinib and 63% and 54% receiving a second-generation TKI first line. MMR and DMR were also observed in 77% and 44% of evaluable patients with ≥13 months' follow-up receiving a second-generation TKI second line. We found little evidence that cardiovascular risk factors were considered during TKI management. These findings highlight key areas for improvement in providing optimal care to patients with CML.

Keywords: tyrosine kinase inhibitor, chronic myeloid leukaemia, real-world study, molecular response, management

Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionised outcomes for patients with chronic myeloid leukaemia in chronic phase (CML-CP), with survival rates approaching those of the general population (Bower *et al*, 2016; Hoglund *et al*, 2013; Sasaki *et al*, 2015). Consequently, key considerations for optimal patient care have evolved considerably. While the primary aim remains achievement of molecular response that minimises the risk of disease progression (Baccarani *et al*, 2013), increasingly, complications of the treatment need to be considered. It is therefore essential for physicians to understand the best use of the available ABL1-targeting TKIs (Baccarani *et al*, 2013). This is the principal purpose of ~~of the most recent~~the 2013 European LeukemiaNet (ELN) recommendations, which increased focus on molecular responses at 3, 6 and 12 months, with patients' responses categorized as optimal, warning or failure (Baccarani *et al*, 2013). Patients experiencing failure are at particular risk of disease progression, and the guidelines recommend that such patients switch treatment and undergo assessment for *BCR-ABL1* kinase domain mutations (Baccarani *et al*, 2013).

While the ~~current~~ ELN 2013 guidelines state that patients must achieve a major molecular response (MMR; *BCR-ABL1* ≤0.1% on the International Scale [IS]) by 12 months for their response to be considered optimal (Baccarani *et al*, 2013), deeper levels of response, including MR^4 (*BCR-ABL1*^{IS} ≤0.01%) and $MR^{4.5}$ (*BCR-ABL1*^{IS} ≤0.0032%), are also recognized as important milestones (Cross *et al*, 2012; Etienne *et al*, 2014; Hehlmann *et al*, 2014). Some patients with a sustained deep molecular response (DMR; MR^4 or better) may be eligible to attempt treatment-free remission (TFR) (Hochhaus *et al*, 2017b; Mahon, 2017; NCCN, 2020; Rea *et al*, 2018). Clinical trials have demonstrated that patients are more likely to achieve

optimal and deeper responses to first-line therapy at key ELN milestones when second-generation (2G) TKIs are used rather than imatinib; however, achievement of responses in real-world practice is less well studied, particularly in the second-line setting (Cortes *et al,* 2018a; Cortes *et al*, 2016; Hochhaus *et al*, 2016). Achievement of ELN-defined responses and how ELN guidelines are implemented in real-world settings are infrequently explored.

An increased risk of cardiovascular (CV) adverse events (AEs) has been described in patients receiving 2G- or third-generation–TKIs compared with imatinib, especially in patients with pre-existing CV risk factors (Chai-Adisaksopha *et al*, 2016; Cortes *et al*, 2018b; Cortes *et al*, 2016; Hochhaus *et al*, 2016; Lipton *et al*, 2016). Given the excellent long-term outcomes in CML, comorbidities are now a major consideration (Jabbour *et al*, 2014; Saussele *et al*, 2015). However, in UK routine clinical practice, it is unclear how physicians assess and manage CV risk factors or how CV risk factors affect TKI management.

UK TARGET CML (CAMN107CGB12) is a retrospective observational study of baseline assessment of patients with CML-CP, TKI treatment pathways, response monitoring patterns and response rates in routine UK National Health Service (NHS) clinical practice; we compared findings with ELN 2013 recommendations (Baccarani *et al*, 2013).

Methods

Study design

This retrospective noninterventional study was conducted at 21 UK NHS secondary and tertiary care centres. Data were collected from paper and electronic records. Inclusion criteria included

CML-CP diagnosis at start of first-line TKI, age ≥18 years and ≥6 months of follow-up from date of first TKI (between January 2013 and April 2017). Patients prescribed first TKI in a clinical trial and patients in accelerated phase (AP) or blast phase (BP) before initiation of first TKI were excluded.

Objectives were to describe TKI treatment pathways in the UK, patient characteristics, practices for assessing and managing CV risk factors before TKI treatment, responses to first- and second-line TKI therapy at ELN time points, recorded reasons for stopping/changing TKIs, adherence to ELN 2013 recommendations and disease progression frequency and management. AE data were not collected.

Data were analysed using descriptive statistics, with a cutoff date of June 6, 2018, using Microsoft Excel and STATA (version 13; StataCorp LLC, College Station, TX, USA). A study size of 200-250 patients in approximately 20 centres (maximum of 40 patients/centre) was expected to give a representative sample of patients in the UK and provide reliable quantitative and qualitative variables.

For comparison with ELN, where data were available, rResponses were categorised as optimal, warning or failure according to ELN 2013 recommendations (Baccarani *et al*, 2013). If *BCR-ABL1* transcript levels were not available on the IS, unconverted *BCR-ABL1*/*ABL1* percentages were used to reflect real-world practices at that centre (all centres used *ABL1* as a reference gene). Two of 14 centres (14%) reported on the IS in 2013; increasing to 17/21 (81%) in 2017.

Results

Patient demographics and baseline characteristics

Two-hundred-fifty-seven patients (186 from 14 tertiary centres and 71 from 7 general hospitals) were enrolled between November 2015 and September 2017. Median follow-up by the data cutoff was 32.9 months (range, 12.6-58.6). Baseline characteristics are shown in **Table I**. Clinical characteristics (other than white blood cell counts) and risk scores at diagnosis were not well documented.

The first-line TKI was imatinib in the majority of patients (79%); reasons for first-line TKI choice were recorded for <50% of patients: clinician preference, "standard first-line choice" and "good results expected" were the most frequently cited reasons (**Supplementary Table I**). First-line imatinib and 2G-TKIs were prescribed to 31/42 (74%) and 11/42 (26%) patients with high Sokal scores, respectively, and 23/34 (68%) and 11/34 (32%) with high European Treatment and Outcomes Study (EUTOS) scores. Patients receiving a first-line 2G-TKI were younger (median, 46 years [95% CI, 41-53 years] than those receiving first-line imatinib (median, 55 years [95% CI, 52-59 years]; Mann-Whitney U test, $P = 0.0128$).

CV risk factors and other documented comorbidities at baseline

Among all patients, 149 (58%) had ≥1 recorded comorbidity at baseline (**Table I**). Seventy-four patients (36%) receiving imatinib had CV comorbidities at baseline vs 7 (13%) receiving a 2G-TKI (**Table II**). Only 74 patients (29%) had baseline blood pressure documented; 33 (45%) had stage ≥2 hypertension (**Supplementary Table II**) (Whelton *et al*, 2018).

Exact levels of baseline blood glucose were documented in 58 patients (23%); documentation occurred more often in patients treated with first-line 2G-TKI (20/54 [37%]) vs imatinib (38/203 [19%]). Baseline low-density lipoprotein and total cholesterol levels were recorded in 23 (9%) and 40 (16%) patients. CV risk assessment tool use was documented for 10 patients (4%), with the validated QRISK2 tool used in 3 (1%).

Response monitoring practices

Within 12 months of starting first-line TKI, 250 patients (97%) had ≥1 real-time quantitative polymerase chain reaction (RQ-PCR) assessment and 221 patients (86%) had ≥3 RQ-PCR assessments. Two-hundred-four (79%), 177 (69%), and 162 (63%) patients had assessments at the 3-, 6-, or 12-month ELN milestones (regardless of TKI line), respectively. Cytogenetic testing (chromosome banding analysis or fluorescence in situ hybridization) was conducted less frequently. Frequency of assessments at ELN milestones on first and second TKI are described in **Table III**.

First-line TKI therapy

Median follow-up duration on first-line TKI and molecular responses to first-line TKI therapy are shown in **Table IV**. Time to discontinuation of first TKI for patients on imatinib vs 2G-TKI is shown in **Fig 1**. For patients receiving imatinib or nilotinib, respective median starting doses were 400 or 600 mg/day; 24/203 (12%) and 8/50 (16%) had dose reductions, while 14% and 12% had dose interruptions.

Quantifiable molecular or cytogenetic assessments were performed at ≥1 ELN milestone during first-line TKI in 223 patients (87%) (**Fig 2**). Forty-eight patients had ≥1 failure; 11 (23%) remained on first-line TKI (median follow-up, 13.8 months [interquartile range (IQR), 12.8-25.9]), and 37 (77%) switched TKIs (median follow-up, 25.1 months [IQR, 14.3-32.6]).

Second-line TKI therapy

At least one TKI switch occurred in 113 patients (44%); 54 (21%) switched more than once. Reasons for the first switch were resistance in 73 (65%), intolerance in 38 (34%) and other reasons in 2 (2%) (**Supplementary Table III**). ~~*BCR-ABL1* kinase domain mutational analysis was performed prior to the first switch in 24 patients (21%), including 20 (27%) who switched due to resistance and 4 (10%) who switched due to intolerance or other reasons.~~ Thirteen patients (12%) switched to imatinib, 68 (60%) to nilotinib, 20 (18%) to dasatinib, 11 (10%) to bosutinib and one (1%) to ponatinib (**Supplementary Table IV)**. For patients receiving second-line imatinib, nilotinib, dasatinib and bosutinib, median starting doses (range) were 400 (200-400), 600 (200-800), 100 (50-100) and 300 (100-500) mg/day, respectively.

Median follow-up duration after switching to second TKI was 23.7 months (range, 1.2-54.1) (**Table V**). MMR at any time and DMR at any time were observed in 37/51 (73%) and 21/51 (41%) patients with ≥13 months' follow-up on second line. Molecular responses to second-line TKI for all patients regardless of follow-up duration are shown in **Supplementary Table V**.

Of 113 patients who switched TKI at least once, 18 (16%) had failure on second-line TKI (**Supplementary Fig 1**); 7 (39%) remained on that TKI (median follow-up, 24.3 months [IQR, 11.6-31.0]), while 11 (61%) switched again (median follow-up, 27.5 months [IQR, 16.4-33.8]).

Kinase domain mutation analysis

BCR-ABL1 kinase domain mutational analysis was performed prior to the first switch in 24 patients (21%), including 20 (27%) who switched due to resistance and 4 (10%) who switched due to intolerance or other reasons. Clinically actionable mutations were identified in 6 patients **(Supplementary Table VI).**

Overall TKI pathways

Among all patients, 144 (56%) received only a first-line TKI, and 59 (23%), 35 (14%), 16 (6%) and 3 (1%) received 2, 3, 4 and 5 TKIs, respectively; sequences of TKI received are described in **Supplementary Table IV**. Eleven patients received the same TKI in multiple lines of therapy.

Disease progression

Ten patients progressed to AP and/or BP, and 15 patients died (10 in CP and 5 after progression). Survival outcomes and treatments to manage progression are summarized in **Fig 3**.

Discussion

The management of CML has undergone dramatic changes; however, it remains unclear whether real-world practice in the UK has evolved with these developments. We conducted the UK TARGET CML study to assess this question, with a particular focus on (1) TKI treatment

pathways, (2) implementation of ELN recommendations for molecular-based patient management, (3) attainment of DMR with first- and second-line TKI in real-world practice and (4) assessment of baseline CV risk factors.

Despite relatively short median follow-up (<33 months), almost half of patients switched from first-line TKI, most often due to resistance (65%). In addition, 21% of patients received ≥3 lines of TKIs. This frequency of TKI switching was somewhat higher than that observed in prospective clinical trials, such as the pivotal trial of frontline imatinib (International Randomized Study of Interferon and STI571 [IRIS]), which reported that 34% of patients discontinued treatment after 6 years of follow-up, although no other alternative TKI was available at the time of IRIS recruitment (Hochhaus *et al*, 2009). In IRIS long-term follow-up (median, 10.9 years), imatinib discontinuation was most frequently attributed to unsatisfactory therapeutic effect (15.9%), withdrawal of consent (10.3%), or AEs (6.9%) (Hochhaus *et al*, 2017a). Similarly, in the frontline trial of nilotinib (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients [ENESTnd]), treatment discontinuations were most frequently due to suboptimal response/treatment failure or AEs/abnormal laboratory values (12% each by the 5-year data cutoff among patients allocated to nilotinib 300 mg twice daily) (Hochhaus *et al*, 2016). We found that in real-world practice, approximately half of patients required a change of TKI, highlighting the importance of optimal monitoring of molecular responses and treatment-related side effects to ensure proper use of TKIs and timely switching. These data also demonstrated the ongoing challenge of establishing a satisfactory, long-term treatment, with multiple TKI switches being common.

Although 58% of patients had a recorded comorbidity, patients generally had poorly documented baseline clinical characteristics and prognostic scores. Demographic and baseline characteristics were not dissimilar from those of other real-world cohorts (Goldberg *et al*, 2017; Hoglund *et al*, 2013; Nesr *et al*, 2018), although prognostic scores were better documented (98%) in the Swedish CML registry (Hoglund *et al*, 2013). CV events have been reported to be increased with 2G-TKIs (Chai-Adisaksopha *et al*, 2016; Cortes *et al*, 2016; Hochhaus *et al*, 2016), and CV risk factors should therefore be carefully considered when choosing a TKI. Even with first-line imatinib, it is important to assess CV risk given that approximately half of patients will require a switch to a 2G-TKI at some point. Although late complications with 2G-TKIs were not fully understood or evaluable at the time of ELN 2013, the guidelines nevertheless recommended continued clinical monitoring of all patients. Several CV risk factors were very poorly documented in our cohort, and any use of validated CV risk tools, such as QRISK2, was rarely documented. Baseline blood pressure was documented in fewer than one-third of patients; when baseline blood pressure was recorded, it was often elevated, with 3 patients in hypertensive crisis, illustrating the importance of documenting this parameter so that hypertension can be managed appropriately. However, some evidence was observed that CV comorbidities at baseline played a role in first-line TKI choice, with patients appearing more likely to receive first-line imatinib if a CV comorbidity was documented.

Currently, the UK National Institute for Health and Care Excellence (NICE) recommends NHS funding in England of imatinib, nilotinib or dasatinib in the first line and nilotinib, dasatinib, bosutinib or ponatinib in later lines (NICE, 2018). In this cohort, first-line treatment was mostly imatinib or nilotinib (<2% received first-line dasatinib), and second-line treatment was mostly

nilotinib, reflecting NICE recommendations at the start of treatment for these patients (dasatinib was not routinely available). Patients were more likely to receive first-line 2G-TKIs than imatinib if they were younger and had no documented comorbidities. Overall, prognostic scores were poorly documented despite strong evidence that these risk scores remain highly predictive of disease response in the TKI era (Hochhaus *et al*, 2016). We did not find evidence that prognostic scores played a major role in first-line TKI choice, with a majority of patients identified as high risk by Sokal, EUTOS or Hasford criteria being treated with imatinib. Overall, 4% of patients progressed to AP and/or BP, corresponding well with the results of the Swedish CML registry (3% by 12 months) (Hoglund *et al*, 2013).

One key finding of this study is that ELN 2013 monitoring recommendations were not consistently implemented. Patients frequently did not have assessments at recommended time points. This finding is consistent with those from the SIMPLICITY study, which reported that monitoring was conducted less frequently than recommended, although with higher frequency in Europe than the United States (Goldberg *et al*, 2017). This finding is important because a previous study showed that patients without frequent molecular monitoring were at higher risk of disease progression (Goldberg *et al*, 2013). In addition, frequent molecular monitoring (3-4 times per year) was associated with greater TKI treatment adherence in patients with CML (Guerin *et al*, 2014).

Overall, in our study, 86% of patients had ≥3 molecular response tests during their first year of TKI treatment, while SIMPLICITY reported 46% for Europe (Goldberg *et al*, 2017), a finding that potentially reflects UK-specific practice or changes in practice over time (UK patients who

were first treated in 2013-2017 were compared with SIMPLICITY patients first treated in 2010-2015). Furthermore, our UK study observed a relatively high level of testing for early molecular response (EMR) at 3 months (81%) compared with SIMPLICITY (32%), indicating rapid adoption of molecular monitoring at early milestones in the UK (Goldberg *et al*, 2017).

However, despite a generous 1-month window applied around ELN milestones, a large proportion of patients (≈20%-30%) were still without evaluable molecular or cytogenetic test results at any given time point during their first year of TKI treatment. Moreover, 13% of patients had no evaluable molecular or cytogenetic result at any ELN milestone during the first year of TKI treatment.

ELN recommended that a patient with ELN-defined failure should have their TKI switched to reduce the risk of progression. Nevertheless, a number of patients in TARGET remained on first-line TKI despite ELN-defined treatment failure.

Strikingly, *BCR-ABL1* kinase domain mutational analyses, recommended by ELN in warning or failure, were infrequently performed, even in patients with documented resistance, despite the known importance of mutation status for subsequent TKI selection. Patients did not always have recommended baseline assessments such as qualitative PCR despite its importance in determining *BCR-ABL1* transcript type, which can affect future molecular monitoring, especially at the low levels before consideration for TFR. Furthermore, although bone marrow and cytogenetic analysis still have an essential role in assessment of patients at baseline, many patients were managed without bone marrow or cytogenetic analysis. Bone marrow evaluation

before TKI switching was infrequently performed, which may reflect the current use of PCR thresholds for interpretation of resistance.

Clinical trials have shown that 2G-TKIs lead to improved rates of molecular responses compared with imatinib (Cortes *et al*, 2018a; Cortes *et al*, 2016; Hochhaus *et al*, 2016). In this cohort, observed rates of EMR and MMR at ELN milestones and DMR at any time during first-line TKI were higher with 2G-TKIs than with imatinib, confirming the results in this real-world setting. While EMR and MMR were defined as optimal responses in ELN 2013 (Baccarani *et al*, 2013), treatment goals are evolving to include deeper responses and TFR (Hochhaus *et al*, 2017b; NCCN, 2020; Rea *et al*, 2018). Studies have shown that deeper molecular responses were associated with improved outcomes compared with complete cytogenetic response (Etienne *et al*, 2014; Hehlmann *et al*, 2014), and a sustained DMR is a prerequisite for attempting TFR in both clinical practice guidelines (Hochhaus *et al*, 2017b; NCCN, 2020; Rea *et al*, 2018) and clinical trials (Mahon *et al*, 2018; Ross *et al*, 2018). Clinical studies have demonstrated that 2G-TKIs can also lead to improved rates of DMR in the second line (Hughes *et al*, 2017). Results from our study showed that patients switching from first-line treatment may achieve not only optimal responses but also deeper responses, including patients with prior resistance or ELN-defined failure.

A criticism of observational studies is the increased risk of selection bias and confounding, precluding the robust analysis and conclusions provided by randomized controlled trials. However, real-world evidence plays an important role in allowing physicians to reflect on current practice. Our study demonstrated that almost half of patients required TKI switch in real-

world practice and that optimal and deep responses can be achieved by patients who switch. However, inadequate CV risk assessment, response monitoring, and mutational analysis increased the risk of inappropriate patient management and, as such, the findings of this study highlighted key areas for improvement in care for patients with CML. Further consideration for improving implementation of guidelines in real-world clinical practice, including very recent updates to the ELN recommendations (Hochhaus *et al* 2020), is warranted.

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Author contributions

AJM and DM designed the research study, performed the research, analysed the data and wrote the paper. REC and PN designed the research study, performed the research and analysed the

data. JR and FG designed the research study, analysed the data and wrote the paper. NCPC, LF and SJC designed the research and analysed the data. FWa, JB, FLD, SA, MD, JT, MFM, GC, BH, FWi, MS, MR and SM performed the research and analysed the data.

Competing interests

AJM participated in advisory boards for Novartis, Bristol-Myers Squibb (BMS) and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis. REC participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis, BMS and Pfizer. NCPC participated in advisory boards for Novartis, BMS and Pfizer; received honoraria from Novartis, BMS, Pfizer and Ariad/Incyte; and received research funding from Novartis, BMS and Pfizer. FLD received honoraria, travel, accommodations and expenses from Novartis and Pfizer. MFM participated in advisory boards for Novartis and received honoraria from Novartis, Pfizer and BMS. SM participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis. FWa received educational grants from Pfizer and Novartis. MR participated in advisory boards and received honoraria from Novartis. JB participated in advisory boards and received honoraria from Novartis, Pfizer and Incyte. SA participated in advisory boards and received honorarium, travel and accommodations from Novartis. MD received honoraria from Novartis and Pfizer and research funding from Novartis. JT received support for conference attendance from Novartis. BH participated in advisory boards for Novartis, Pfizer and BMS. FWi received honoraria, travel, accommodation and expenses from Novartis. DM received honoraria from Incyte, Novartis, Pfizer and BMS. JR and SJC are employees and shareholders of Novartis. LF is a

former employee and shareholder of Novartis. FG is an employee of OPEN VIE contracted by Novartis. PN, MS and GC declared no conflict of interest.

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Table I. Patient demographics and baseline characteristics

	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)	First-line nilotinib (n=50)
Sex, n (%)				
Male	144 (56)	119 (59)	25 (46)	24 (48)
Female	113 (44)	84 (41)	29 (54)	26 (52)
Age at initiation of first-line TKI, median (range [IQR]), years	53.5 (18.4-92.4 [38.8-65.8])	55.4 (18.4-92.4 [39.9-67.4])	45.8 (20.3-79.5 [36.4-59.6])	45.1 (20.3-79.5 [36.1-59.6])
Time from CML diagnosis to start of first TKI, median (IQR), days	7.0 (1.0-20.0)	8.0 (2.0-20.3)	6.0 (1.0-11.0)	6.0 (1.0-11.0)
Assessments prior to first-line TKI, n (%)				
RQ-PCR	169 (66)	140 (69)	29 (54)	26 (52)
Qualitative PCR (b2a2, b3a2, other)	140 (54)	107 (53)	33 (61)	30 (60)
CBA	180 (70)	146 (72)	34 (63)	31 (62)
FISH	155 (60)	117 (58)	38 (70)	34 (68)
CBA or FISH (bone marrow)	154 (60)	119 (59)	35 (65)	32 (64)
CBA or FISH (peripheral blood)	54 (21)	45 (22)	9 (17)	9 (18)
Both CBA/FISH and RQ-PCR	139 (54)	117 (58)	22 (41)	20 (40)
Treatment for CML prior to first-line TKI, n (%)				
Yes	126 (49)	97 (48)	29 (54)	26 (52)
Prior treatment[a,b]				
Hydroxycarbamide	116 (92)	89 (92)	27 (93)	24 (92)
Leukapheresis	2 (2)	2 (2)	0	0
Anagrelide	1 (1)	1 (1)	0	0
Interferon	1 (1)	1 (1)	0	0
Aspirin	1 (1)	0	1 (3)	1 (4)
No	128 (50)	104 (51)	24 (44)	23 (46)
Unknown	3 (1)	2 (1)	1 (2)	1 (2)
Ph chromosome at baseline				
Yes	212 (82)	175 (86)	37 (69)	35 (70)
No	3 (1)	1 (<1)	2 (4)	2 (4)
Unknown	42 (16)	27 (13)	15 (28)	13 (26)
Clinical characteristics				
WBC count, median (IQR), 10^9/l	82.4 (31.2-177.3)	77.0 (31.2-158.0)	92.9 (32.3-201.4)	92.1 (32.5-198.9)
Unknown, n (%)[c]	4 (2)	1 (<1)	3 (6)	2 (4)
Platelet count, median (IQR), 10^9/l	404.0 (252.5-603.0)	393.5 (244.8-603.0)	439.0 (339.0-578.0)	441.0 (342.8-589.3)
Unknown, n (%)[c]	14 (5)	11 (5)	3 (6)	2 (4)
Basophils, median (IQR), %	3.9 (2.0-7.0)	3.3 (2.0-6.0)	5.0 (2.3-8.0)	4.0 (2.3-8.3)
Unknown, n (%)[c]	59 (23)	46 (23)	13 (24)	13 (26)
Eosinophils, median (IQR), %	2.0 (1.1-3.7)	2.0 (1.1-3.5)	2.0 (1.3-3.7)	2.0 (1.3-3.0)
Unknown, n (%)[c]	58 (23)	45 (22)	13 (24)	13 (26)
Blasts, median (IQR) (%)	2.0 (1.0-4.8)	2.0 (1.0-3.4)	3.0 (1.6-8.4)	3.0 (1.5-6.0)
Unknown, n (%)[c]	101 (39)	77 (38)	24 (44)	23 (46)
Spleen size below costal margin, median (IQR), cm[d]	1.3 (0.0-10.1)	1.0 (0.0-10.1)	4.0 (0.0-10.3)	2.0 (0.0-10.0)
Unknown, n (%)[c]	85 (33)	67 (33)	18 (33)	17 (34)
Sokal risk score, n (%)[e]				
Low risk	52 (20)	43 (21)	9 (17)	8 (16)
Intermediate risk	54 (21)	41 (20)	13 (24)	13 (26)
High risk	42 (16)	31 (15)	11 (20)	9 (18)

No score recorded and required components not all recorded	109 (42)	88 (43)	21 (39)	20 (40)
EUTOS score, n (%)[f]				
Low risk	110 (43)	90 (44)	20 (37)	19 (38)
High risk	34 (13)	23 (11)	11 (20)	9 (18)
No score recorded and required components not all recorded[g]	113 (44)	90 (44)	23 (43)	22 (44)
Hasford score, n (%)[h]				
Low risk	25 (10)	19 (9)	6 (11)	5 (10)
Intermediate risk	35 (14)	32 (16)	3 (6)	3 (6)
High risk	19 (7)	13 (6)	6 (11)	4 (8)
No score recorded and required components not all recorded	178 (69)	139 (68)	39 (72)	38 (76)
Comorbidities, n (%)				
None recorded	108 (42)	80 (39)	28 (52)	26 (52)
≥1 recorded[i,j]	149 (58)	123 (61)	26 (48)	24 (48)
CV comorbidities	81 (32)	74 (36)	7 (13)	6 (12)
Diabetes	25 (10)	21 (10)	4 (7)	4 (8)
Respiratory disease	20 (8)	17 (8)	3 (6)	3 (6)
Renal disease	16 (6)	14 (7)	2 (4)	2 (4)
Non-haematological cancer	9 (4)	8 (4)	1 (2)	1 (2)
Hepatic disease	4 (2)	3 (1)	1 (2)	1 (2)
Other	86 (33)	70 (34)	16 (30)	15 (30)

2G-TKI, second-generation tyrosine kinase inhibitor; CBA, chromosome banding analysis; CML, chronic myeloid leukaemia; CV, cardiovascular; EUTOS, European Treatment and Outcomes Study; FISH, fluorescence in situ hybridization; IQR, interquartile range; Ph, Philadelphia chromosome; RQ-PCR, real-time quantitative polymerase chain reaction; WBC, white blood cell.

[a] Patients may have received multiple prior treatments.

[b] Proportion of patients with each prior treatment was calculated out of the total number of patients who received prior treatment.

[c] Proportion of patients with unknown clinical characteristics was calculated out of the total number of patients in each column.

[d] Spleens reported to be "normal" or "nonpalpable" were considered to be 0 cm below the costal margin.

[e] Among 148 patients who received any first-line TKI and had an available Sokal risk score at diagnosis, the score was documented for 96 (65%) and not documented and instead calculated during this analysis for 52 (35%).

[f] Among 144 patients who received any first-line TKI and had an available EUTOS risk score at diagnosis, the score was documented for 36 (25%) and not documented and instead calculated during this analysis for 108 (75%).

[g] Includes patients who had a risk category recorded but no score recorded.

[h] Hasford scores were not collected in case report forms and were calculated if required data were available.

[i] Patients may have had multiple comorbidities.

[j] Proportion of patients with each comorbidity was calculated out of the total number of patients in each column.

Table II. Baseline CV comorbidities and risk factors

n (%)	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)	First-line nilotinib (n=50)
Diabetes	25 (10)	21 (10)	4 (7)	4 (8)
Smoking				
Documented[a]	174 (68)	140 (69)	34 (63)	32 (64)
Current smoker	38 (22)	35 (25)	3 (9)	3 (9)
Ex-smoker	46 (26)	39 (28)	7 (21)	6 (19)
Never smoked	88 (51)	65 (46)	23 (68)	22 (69)
Unclear	2 (1)[b]	1 (1)[b]	1 (3)[b]	1 (3)[b]
BMI >30 documented	16 (6)	14 (7)	2 (4)	2 (4)
CV comorbidities				
None recorded	176 (68)	129 (64)	47 (87)	44 (88)
≥1 recorded[c,d]	81 (32)	74 (36)	7 (13)	6 (12)
Hypertension	58 (23)	52 (26)	6 (11)	5 (10)
Hyperlipidaemia	28 (11)	26 (13)	2 (4)	2 (4)
Coronary artery disease	14 (5)	12 (6)	2 (4)	2 (4)
Myocardial infarction	11 (4)	10 (5)	1 (2)	1 (2)
Coronary artery bypass graft	9 (4)	8 (4)	1 (2)	1 (2)
Arrhythmias	8 (3)	7 (3)	1 (2)	1 (2)
Cerebrovascular accident	4 (2)	4 (2)	0	0
Transient ischemic attack	4 (2)	3 (1)	1 (2)	1 (2)
Congestive heart failure	3 (1)	2 (1)	1 (2)	1 (2)
Unstable angina	2 (1)	2 (1)	0	0
Percutaneous coronary intervention	2 (1)	2 (1)	0	0
Peripheral vascular disease	2 (1)	2 (1)	0	0
History of CV disease				
Not documented	101 (39)	80 (39)	21 (39)	20 (40)
Documentation unknown[e]	1 (<1)	1 (<1)	0	0
Documented[f]	155 (60)	122 (60)	33 (61)	30 (60)
No history	26 (17)	23 (19)	3 (9)	3 (10)
Details of history not provided	104 (67)	76 (62)	28 (85)	25 (83)
Details of history provided	25 (16)	23 (19)	2 (6)	2 (7)
Family history of CV disease				
Not documented	159 (62)	128 (63)	31 (57)	29 (58)
Documentation unknown[e]	1 (<1)	1 (<1)	0	0
Documented	97 (38)	74 (36)	23 (43)	21 (42)

2G-TKI, second-generation tyrosine kinase inhibitor; BMI, body mass index; CV, cardiovascular.

[a] Proportion of patients in each smoking category was calculated based on the number of patients with documented smoking status.

[b] Two patients were recorded as "does not smoke"; it was unclear whether they were ex-smokers or never smoked.

[c] Patients could be listed as having >1 CV comorbidity.

[d] Proportion of patients with CV comorbidities was calculated based on total number of patients in each column.

[e] One patient was transferred from another hospital prior to TKI treatment; it was unclear if this patient's personal or family history of vascular disease had been documented prior to TKI treatment.

[f] Proportion of patients within each category was calculated based on the number of patients who had documented CV disease history.

Table III. Frequency of molecular and cytogenetic assessments at ELN milestones for patients on first and second TKI

	All patients n (%)	Imatinib first line n (%)	Second-generation first line n (%)	Nilotinib first line n (%)
First TKI				
RQ-PCR				
3 months[a]	180/223 (81)	143/173 (83)	37/50 (74)	35/47 (74)
6 months[b]	141/199 (71)	105/154 (68)	36/45 (80)	34/42 (81)
12 months[c]	117/170 (69)	95/132 (72)	22/38 (58)	21/35 (60)
CBA/FISH				
3 months[a]	15/223 (7)	15/173 (9)	0/50 (0)	0/47 (0)
6 months[b]	9/199 (5)	8/154 (5)	1/45 (2)	1/42 (2)
12 months[c]	2/170 (1)	2/132 (2)	0/38 (0)	0/35 (0)
CBA/FISH and/or RQ-PCR				
3 months[a]	186/223 (83)	148/173 (86)	38/50 (76)	36/47 (77)
6 months[b]	151/199 (76)	114/154 (74)	37/45 (82)	35/42 (83)
12 months[c]	117/170 (69)	95/132 (72)	22/38 (58)	21/35 (60)
Second TKI				
RQ-PCR				
3 months[a]	63/82 (77)	8/10 (80)	55/72 (76)	43/54 (80)
6 months[b]	44/66 (67)	4/8 (50)	40/58 (69)	31/46 (67)
12 months[c]	27/52 (52)	4/8 (50)	23/44 (52)	19/39 (49)
CBA or FISH				
3 months[a]	12/82 (15)	2/10 (20)	10/72 (14)	9/54 (17)
6 months[b]	4/66 (6)	0/8 (0)	4/58 (7)	4/46 (9)
12 months[c]	1/52 (2)	0/8 (0)	1/44 (2)	1/39 (3)
CBA/FISH and/or RQ-PCR				
3 months[a]	65/82 (79)	8/10 (80)	57/72 (79)	45/54 (83)
6 months[b]	45/66 (68)	4/8 (50)	41/58 (71)	32/46 (70)
12 months[c]	27/52 (52)	4/8 (50)	23/44 (52)	19/39 (49)
≥1 assessment at an ELN milestone (first- or second-line TKI)[a]	239/257 (93)	189/203 (93)	50/54 (93)	48/50 (96)

CBA, chromosome banding analysis; ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; RQ-PCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

[a] Denominator included patients with ≥4 months' follow-up on that TKI.

[b] Denominator included patients with ≥7 months' follow-up on that TKI.

[c] Denominator included patients with ≥13 months' follow-up on that TKI.

Table IV. Summary of molecular responses to first-line TKI therapy[a]

	Overall responses			First-line TKI			
	First-line imatinib (n=203)	First-line 2G-TKI (n=54)[b]	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)[b]	First-line nilotinib (n=50)	All patients (N=257)
Median follow-up duration[c] on each TKI (range), months	33.3 (12.6-58.6)	30.0 (13.2-56.8)	32.9 (12.6-58.6)	16.7 (0.5-54.8)	20.8 (0.5-55.3)	21.3 (0.5-55.3)	17.5 (0.5-55.3)
EMR at 3 months (±1 month), in patients with 3-month molecular response assessments, n (%)	88/163 (54)	29/41 (71)	117/204 (57)	88/156 (56)	28/38 (74)	26/36 (72)	116/194 (60)
MMR by 12 months (±1 month), n (%)	84 (41)	28 (52)	112 (44)	71 (35)	26 (48)	25 (50)	97 (38)
MMR at any time, n (%)	156 (77)	42 (78)	198 (77)	102 (50)	34 (63)	32 (64)	136 (53)
DMR at any time, n (%)	95 (47)	35 (65)	130 (51)	58 (29)	29 (54)	27 (54)	87 (34)

2G-TKI, second-generation tyrosine kinase inhibitor; DMR, deep molecular response; EMR, early molecular response; IS, International Scale; MMR, major molecular response.

[a] Patients could appear in multiple molecular response categories. Molecular responses were assessed as EMR (*BCR-ABL1*^{IS} ≤10% at 3 months), MMR (*BCR-ABL1*^{IS} ≤0.1%) by 12 months, MMR at any time and DMR (*BCR-ABL1*^{IS} ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used.

[b] Fifty patients received first-line nilotinib, and 4 received first-line dasatinib.

[c] The columns for overall response reported the duration of follow-up for all TKI therapies, including later-line TKIs in patients who switched from their first-line TKI (from start of first-line TKI to most recent data collection, akin to an intention-to-treat analysis). The columns for first-line TKI therapy reported the duration of follow-up for only first-line TKI therapy (from start of first-line TKI to most recent data collection or death in patients who continued receiving first-line TKI or to end of first-line TKI for patients who switched to a second-line TKI).

Table V. Summary of molecular responses after switching to second-line TKI therapy[a]

	All switched patients (n=113)	Second-line imatinib (n=13)	Second-line 2G-TKI (n=100)[b]	Second-line nilotinib (n=68)	Switched to second line for resistance (n=73)	Switched to second line for intolerance or other reason (n=40)[c]
Median follow-up post first switch (range), months[d]	23.7 (1.2-54.1)	22.5 (4.9-43.0)	23.9 (1.2-54.1)	29.7 (1.2-52.4)	27.4 (1.2-51.4)	20.1 (2.8-54.1)
Median follow-up on second-line TKI (range), months[e]	23.9 (13.6-50.2)	19.2 (13.6-43.0)	28.6 (13.9-50.2)	27.3 (13.9-50.2)	25.6 (13.9-46.5)	20.3 (13.6-50.2)
~~EMR at 3 months (±1 month) in patients with BCR-ABL1 at 3 months, n (%)~~	~~75/85 (88)~~	~~11/11 (100)~~	~~64/74 (86)~~	~~48/53 (91)~~	~~47/55 (85)~~	~~28/30 (93)~~
EMR at 3 months (±1 month) on second TKI in patients with 3-month molecular response assessments, n (%)[f]	59/70 (84)	10/10 (100)	49/60 (82)	38/45 (84)	39/47 (83)	20/23 (87)
MMR by 12 months (±1 month) on second TKI, n (%)[g]	30/50 (60)	4/7 (57)	26/43 (60)	24/38 (63)	21/35 (60)	9/15 (60)
MMR at any time on second TKI, n (%)[g]	37/51 (73)	4/8 (50)	33/43 (77)	29/38 (76)	27/36 (75)	10/15 (67)
DMR at any time on second TKI, n (%)[g]	21/51 (41)	2/8 (25)	19/43 (44)	17/38 (45)	15/36 (42)	6/15 (40)

2G-TKI, second-generation tyrosine kinase inhibitor; DMR, deep molecular response; EMR, early molecular response; IS, International Scale; MMR, major molecular response.

[a] Patients could appear in multiple molecular response categories. Molecular responses after switch to second TKI were assessed as EMR (*BCR-ABL1*^{IS} ≤10% at 3 months), MMR (*BCR-ABL1*^{IS} ≤0.1%) by 12 months, MMR at any time and DMR (*BCR-ABL1*^{IS} ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used.

[b] Switched to 2G-TKI (n=68 nilotinib, n=20 dasatinib, n=11 bosutinib, n=1 ponatinib).

[c] Switched for intolerance (n=38) or switched for another reason (n=2).

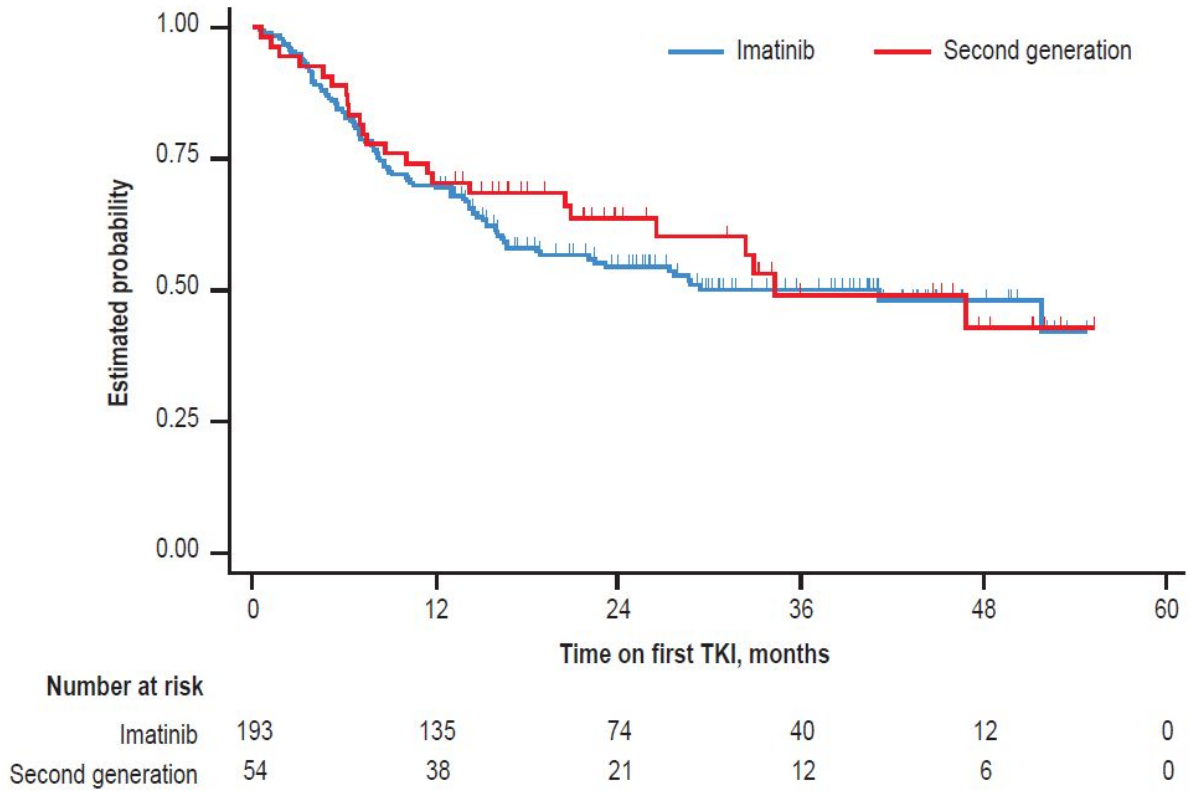
[d] Duration from start of second-line TKI to last data collection or death (included patients with ≥1 switch).

[e] Duration from start of second-line TKI to last data collection, date of switch to a third-line TKI, or death.

[f] EMR defined as *BCR-ABL1*^{IS} ≤10% at 3 months (±1 month); only those patients with *BCR-ABL1* available at 3 months were included.

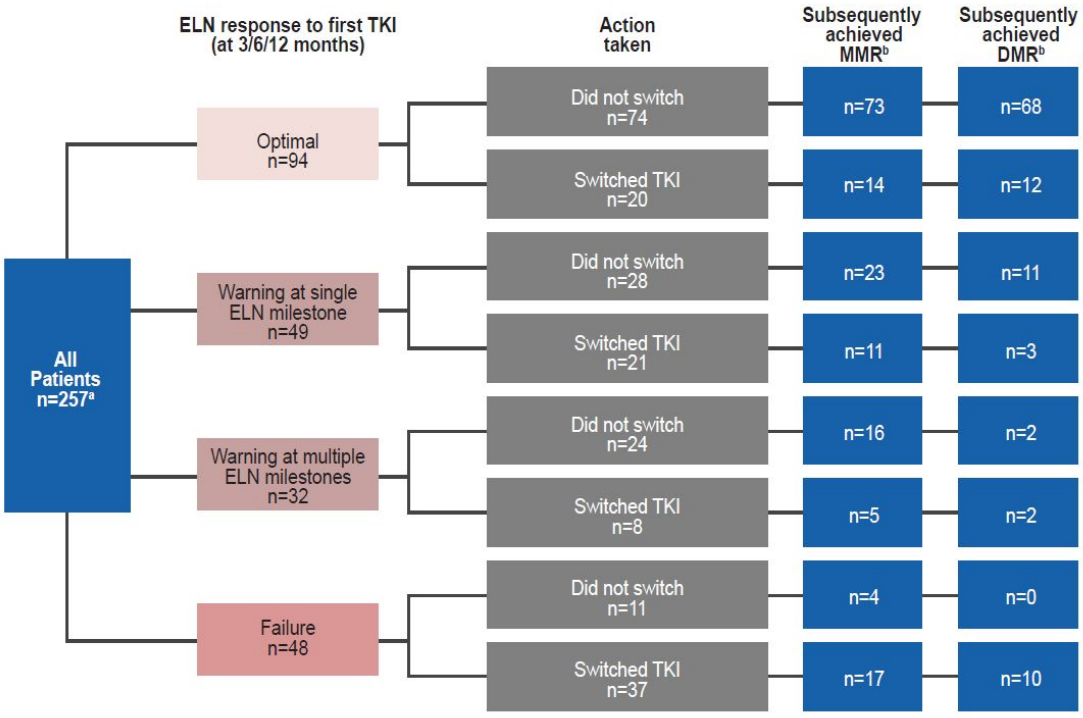
[g] MMR (≤0.1% *BCR-ABL1*); DMR (≤0.01% *BCR-ABL1*); only those patients with ≥13 months' follow-up were included.

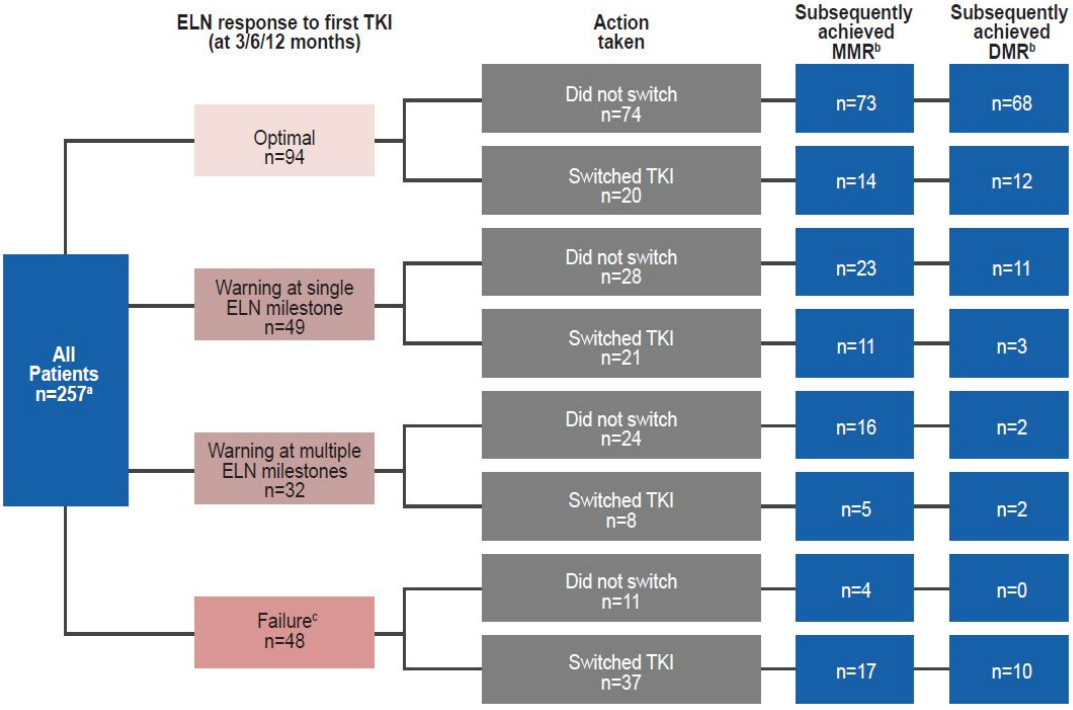
Fig 1. Kaplan-Meier curve: time to discontinuation of first-line TKI



Patients who had not switched from first TKI at point of data collection were censored at date of data collection or death. Months on first TKI were unknown for 10 patients on imatinib. TKI, tyrosine kinase inhibitor.

Fig 2. TKI treatment pathways and molecular responses for patients with ELN optimal, warning (at single vs multiple ELN milestones) or failure responses while on first-line TKI





[a] To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points (3, 6 and 12 months). In patients with multiple test results available, any patient with a failure response to first-line TKI at an ELN milestone (regardless of other responses achieved at earlier milestones) was

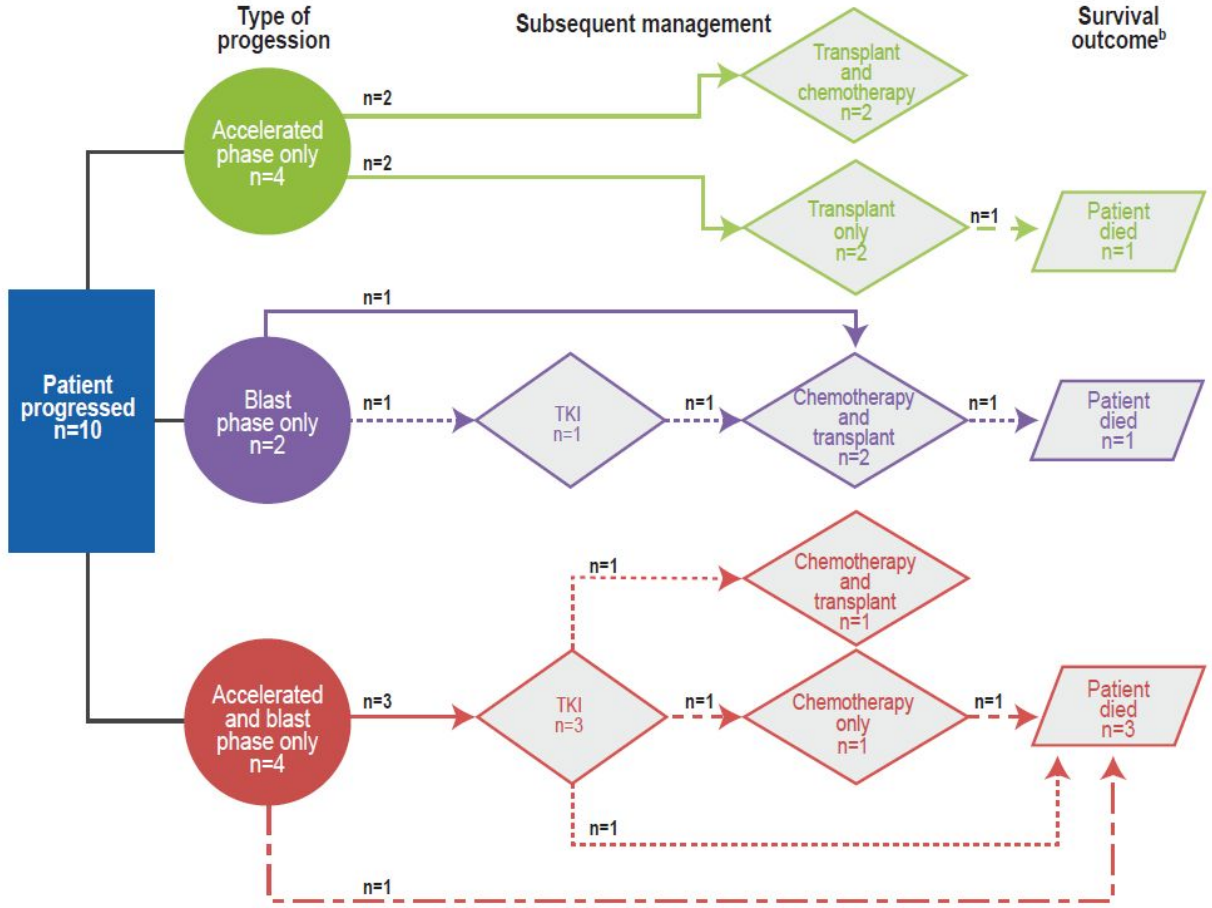
classified as having a failure response~~failure~~. Patients in the optimal category had only optimal responses at an ELN milestone (3, 6 or 12 months) with either molecular or cytogenetic assessment (where a molecular test was not available). Patients in the warning category had a warning at any milestone with either assessment but had no failure at any milestone with either assessment. Patients without assessments at any ELN milestone could not be categorized. Thirty-four patients had no evaluable test at any ELN milestone by either molecular or cytogenetic test.

[b] Response may have been observed at any time. Duration of follow up varied; patient may have had ≥1 subsequent TKI switch. Forty-eight patients had ≥1 failure; 11 (23%) remained on first-line TKI (median follow-up, 13.8 months [IQR, 12.8-25.9 months]), and 37 (77%) switched TKIs (median follow-up, 25.1 months [IQR, 14.3-32.6 months]). Of those who switched, 22 had their first failure at 6 months (*BCR-ABL1*^{IS} range, 10.1%-60.1%; 2 patients had a failure according to FISH), and 15 had their first failure at 12 months (*BCR-ABL1*^{IS} range, 1.2%-12.7%). Among these patients with a failure who switched TKIs, 17 (46%) and 10 (27%) achieved MMR and DMR at any time, respectively, vs 4 (36%) and 0 patients who did not switch TKIs. Of 81 patients with warning but no failure, 52 (64%) remained on first-line TKI (median follow-up 28.4 months [IQR, 13.7-40.4 months]), and 29 (36%) switched TKIs (median follow-up 30.9 months [IQR, 20.3-38.3 months]). Of those who switched TKIs, 19/29 had ≥1 additional RQ-PCR assessment between the initial warning and TKI switch. Of 34 patients without any quantifiable assessment at any ELN milestone, 27 (79%) switched TKIs.

[c] Of 48 patients with ELN-defined failure responses, 39 were treated with imatinib as first-line therapy and 9 with a 2G-TKI; 38 patients (79%) also had an ELN-defined warning at a prior ELN time point (with either a molecular or cytogenetic test).

DMR, deep molecular response; ELN, European LeukemiaNet; EMR, early molecular response; FISH, fluorescence in situ hybridization; IQR, interquartile range; IS, International Scale; MMR, major molecular response; RQ-PCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

Fig 3. Disease progression[a]



[a] Eight patients (7 on imatinib, 1 on a second-generation TKI) progressed to accelerated phase (AP) during the course of the study. The median time to progression was 16.5 months (range, 2.1-31.1; IQR, 7.5-26.4; time to progression was unknown for one patient on first-line imatinib). Three patients had a prior warning response at an ELN milestone (all 3 patients received imatinib as first TKI), and 3 patients had a failure response at an ELN milestone (2 patients received imatinib first line and 1 patient received nilotinib). The other 2 patients who progressed to AP had no prior evaluable response at an ELN milestone (both patients received first-line imatinib). Treatments for progression to AP were TKIs in 3 patients, chemotherapy in 4 patients and allogenic haematopoietic stem cell transplant (HSCT) in 5 patients. Six patients progressed to BP (all received first-line imatinib), including 4 who were previously recorded as progressing to AP. Median time from start of first-line TKI to progression to BP was 22.7 months (range 1.2- 32.1; IQR, 17.2-30.1). Treatments for progression to BP were TKIs in 4 patients, chemotherapy in 4 patients, allogenic HSCT in 2 patients and haploidentical allogenic HSCT in one patient. Among 4 patients who progressed to AP only, 2 received 1 TKI prior to progression, 1 received 3 TKIs prior to progression, and 1 had an unknown date of disease progression. Among 4 patients who progressed to AP and BP, 2 each received 1 or 2 TKIs prior to their earliest progression, respectively. Among 2 patients who progressed to BP only, 1 each received 1 or 2 TKIs prior to progression, respectively. None of the patients who progressed were observed to have only ELN-optimal responses to first-line TKI; 3 patients had ≥1 failure, 4 had ≥1 warning and 2 had no available assessments at ELN milestones. In the 10 patients who progressed to AP and/or BP, baseline Sokal score was recorded as high for 4, intermediate for 2, low for 1 and unknown for 3.

[b] A total of 15/257 patients died during the study observation period; 5 of these patients had progressed to AP and/or BP prior to death (n=4 had blast crisis prior to death). Another 5 patients had progressed but were still alive at data

collection (n=2 had blast crisis); all had received alternative treatment with 4 of 5 receiving both transplant and chemotherapy after progressing (n=1 after alternative TKI); the other patient received a transplant only.
AP, accelerated phase; BP, blast phase; ELN, European LeukemiaNet; TKI, tyrosine kinase inhibitor.

Supplementary Tables/Figures

Supplementary Table I. Reasons for choice of first-line TKI recorded for ≥2% of all patients

Recorded reason, n (%)[a]	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)
Known reasons[b]	113 (44%)	92 (45)	21 (39)
Clinician preference	26 (10)	18 (9)	8 (15)
Standard first-line choice	20 (8)	17 (8)	3 (6)
Good results expected	17 (7)	15 (7)	2 (4)
Ease of administration	9 (4)	9 (4)	0
Ineligibility for clinical trial/no trial available	9 (4)	9 (4)	0
Cardiovascular comorbidities	9 (4)	9 (4)	0
Low risk	7 (3)	7 (3)	0
Tolerability/side effect profile	7 (3)	6 (3)	1 (2)
Perceived as better option compared with others	7 (3)	6 (3)	1 (2)
Patient choice	7 (3)	5 (2)	2 (4)
Local or network guidance	7 (3)	7 (3)	0
Smoker	6 (2)	6 (3)	0
Patient age	3 (1)	3 (1)	0
Diabetes	3 (1)	3 (1)	0
High Sokal risk score	3 (1)	1 (<1)	2 (4)
Renal comorbidities	2 (1)	2 (1)	0
Started treatment in another country (and moved to United Kingdom)	2 (1)	0	2 (4)
Intermediate Sokal risk	1 (<1)	0	1 (2)
Low QRISK	1 (<1)	0	1 (2)
Reasons unknown	144 (56)	111 (55)	33 (61)

2G-TKI, second-generation tyrosine kinase inhibitor.

[a] Percentages were calculated out of total number of patients in each column.

[b] Some patients had multiple reasons recorded.

Supplementary Table II. Baseline blood pressure (Whelton *et al*, 2018)

n (%)	All patients (N=257)	First-line imatinib (n=203)	First-line 2G-TKI (n=54)	First-line nilotinib (n=50)
Documented[a]	74 (29)	62 (31)	12 (22)	11 (22)
Normal (SBP <120 mm Hg and DBP <80 mm Hg)	14 (19)	11 (18)	3 (25)	3 (27)
Elevated (SBP 120-129 mm Hg and DBP <80 mm Hg)	15 (20)	13 (21)	2 (17)	1 (9)
Stage 1 hypertension (SBP 130-139 mm Hg or DBP 80-89 mm Hg)	12 (16)	8 (13)	4 (33)	4 (36)
Stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg)	30 (41)	27 (44)	3 (25)	3 (27)
Hypertensive crisis (SBP >180 mm Hg and/or DBP >120 mm Hg)	3 (4)	3 (5)	0	0
Not documented	182 (71)	140 (69)	42 (78)	39 (78)
Not known whether documented	1 (<1)[b]	1 (<1)[b]	0	0

2G-TKI, second-generation tyrosine kinase inhibitor; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] Proportion of patients in each blood pressure category is calculated out of the number of patients with documented blood pressure.

[b] One patient was transferred from another hospital prior to TKI treatment; it was unclear if this patient's blood pressure had been documented prior to TKI treatment.

Supplementary Table III. Reasons for switch from first-line TKI

n (%)[a]	Patients who switched from first-line TKI (n=113)[b]
Resistance[c]	73 (65)
Intolerance or other reasons	40 (35)
Intolerance	38 (34)
Other reasons[d]	2 (2)

TKI, tyrosine kinase inhibitor.

[a] Proportions were calculated based on the total number of patients who switched from first-line TKI.

[b] Among these patients, 40% (45 of 113) had mutation detection done at any time before or after switching, and 19% (21 of 113) had mutation analysis done after the first switch; of those, 16 patients were switched due to resistance, and 5 patients were switched due to intolerance or other reasons.

[c] Group classified as resistance based on documented failure, resistance or lack/loss of efficacy, including patients with resistance and patients with resistance and intolerance. The intolerance group included patients who switched for intolerance only.

[d] Other reasons for switch were listed as they were recorded.

Supplementary Table IV. Overall TKI pathways

Total TKIs, n	Patients, n	TKIs received					Patients, n	% (n=257)
		First line	Second line	Third line	Fourth line	Fifth line		
1	144	Imatinib					112	43.6
		Nilotinib					29	11.3
		Dasatinib					3	1.2
2	59	Imatinib	Nilotinib				37	14.4
		Imatinib	Dasatinib				5	1.9
		Imatinib	Bosutinib				5	1.9
		Nilotinib	Imatinib				6	2.3
		Nilotinib	Dasatinib				2	0.8
		Nilotinib	Bosutinib				3	1.2
		Nilotinib	Ponatinib				1	0.4
3	35	Imatinib	Nilotinib	Dasatinib			12	4.7
		Imatinib	Nilotinib	Bosutinib			8	3.1
		Imatinib	Nilotinib	Imatinib			1	0.4
		Imatinib	Dasatinib	Bosutinib			3	1.2
		Imatinib	Dasatinib	Nilotinib			2	0.8
		Imatinib	Dasatinib	Ponatinib			2	0.8
		Imatinib	Dasatinib	Imatinib			1	0.4
		Imatinib	Bosutinib	Nilotinib			1	0.4
		Nilotinib	Imatinib	Dasatinib			2	0.8
		Nilotinib	Imatinib	Bosutinib			2	0.8
		Nilotinib	Imatinib	Nilotinib			1	0.4
4	16	Imatinib	Nilotinib	Dasatinib	Bosutinib		3	1.2
		Imatinib	Nilotinib	Dasatinib	Ponatinib		3	1.2
		Imatinib	Nilotinib	Bosutinib	Ponatinib		1	0.4
		Imatinib	Nilotinib	Imatinib	Nilotinib		1	0.4
		Imatinib	Nilotinib	Dasatinib	Imatinib		1	0.4
		Imatinib	Dasatinib	Nilotinib	Imatinib		1	0.4
		Imatinib	Bosutinib	Dasatinib	Imatinib		1	0.4
		Nilotinib	Imatinib	Dasatinib	Bosutinib		1	0.4
		Nilotinib	Imatinib	Bosutinib	Nilotinib		1	0.4
		Nilotinib	Dasatinib	Bosutinib	Ponatinib		1	0.4
		Nilotinib	Dasatinib	Bosutinib	Imatinib		1	0.4
		Dasatinib	Bosutinib	Nilotinib	Imatinib		1	0.4
5	3	Imatinib	Dasatinib	Bosutinib	Ponatinib	Imatinib	1	0.4
		Imatinib	Dasatinib	Bosutinib	Dasatinib	Bosutinib	1	0.4
		Imatinib	Nilotinib	Dasatinib	Nilotinib	Ponatinib	1	0.4

TKI, tyrosine kinase inhibitor.

Supplementary Table V. Summary of molecular responses to second-line TKI therapy in patients[a]

	All patients (n=113)	Imatinib 2L (n=13)	2G-TKI 2L (n=100)	Nilotinib 2L (n=68)	Switched to 2L for resistance (n=73)	Switched to 2L for intolerance/other reason (n=40)
Median follow-up on TKI (range), months	11.1 (0.2-50.2)	15.9 (0.9-43.0)	10.9 (0.2-50.2)	14.5 (0.2-50.2)	27.4 (1.2-51.4)	20.1 (2.8-54.1)
EMR at 3 months (±1 month) in patients with *BCR-ABL1* at 3 months, n (%)	59/70 (84)	10/10 (100)	49/60 (82)	38/45 (84)	39/47 (83)	20/23 (87)
MMR by 12 months (±1 month), n (%)	41/92 (45)	7/12 (58)	34/80 (43)	26/57 (46)	26/61 (43)	15/31 (48)
MMR at any time, n (%)	48/94 (51)	7/13 (54)	41/81 (51)	31/58 (53)	32/62 (52)	16/32 (50)
DMR at any time, n (%)	28/94 (30)	4/13 (31)	24/81 (30)	18/58 (31)	19/62 (31)	9/32 (28)

2G-TKI, second-generation tyrosine kinase inhibitor; 2L, second line; DMR, deep molecular response; ELN, European LeukemiaNet; EMR, early molecular response; IS, International Scale; MMR, major molecular response; RQ-PCR, real-time quantitative polymerase chain reaction.
For EMR, patient was required to have RQ-PCR at 3 months (±1 month).
Molecular response categories were not mutually exclusive; the same patient could appear in multiple response categories.
For MMR/DMR responses, denominator included only those patients with ≥1 RQ-PCR on second line (and by 12 months [±1 month] on second line for the MMR by 12-month responses).
[a] Follow-up period was months from second TKI until switch in patients who switched to third TKI or, in those who did not switch, to data collection or death. Molecular responses were assessed as early molecular response (EMR; *BCR-ABL1*^{IS} ≤10% at 3 months), MMR (*BCR-ABL1*^{IS} ≤0.1%) by 12 months, MMR at any time, and DMR (*BCR-ABL1*^{IS} ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used.

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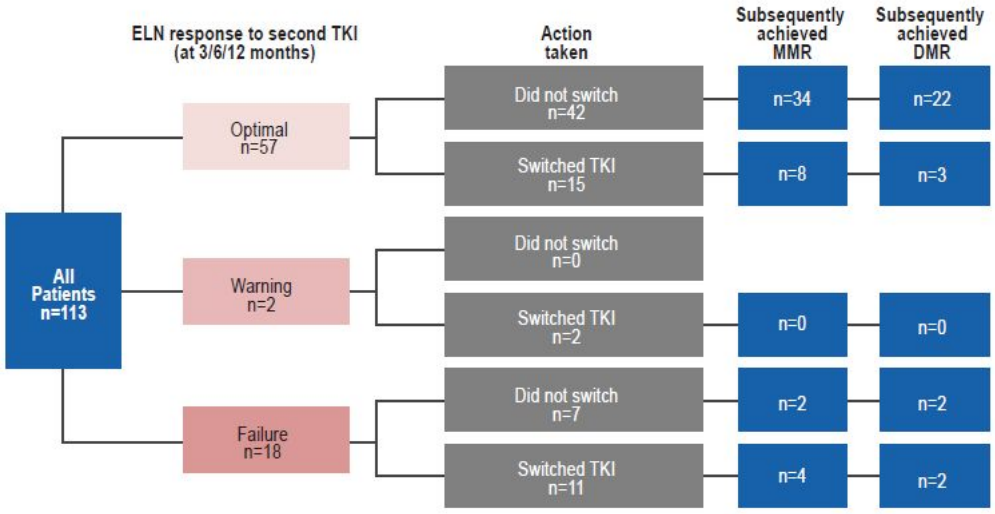
Patient	Details	Actionable mutation (Y/N)	Resistance[b]	2L TKI
1	Q252H	Y	Imatinib	Nilotinib
2	E255V	Y	Imatinib and to lesser extent nilotinib, bosutinib	Dasatinib
3	T315I	Y	All TKIs except ponatinib	Ponatinib
4	E255K F359C	Y	Imatinib and to lesser extent nilotinib, bosutinib	Dasatinib
5	L384M	Y	Imatinib	Nilotinib
6	E255V	Y	Imatinib and to lesser extent nilotinib, bosutinib	Dasatinib

2L, second line; TKI, tyrosine kinase inhibitor.

[a] Among 113 patients who switched TKI, 40% (45 of 113) had mutation detection done at any time before or after switching; 21% (24 of 113) had mutation analysis done before the first switch, and of those, 20 patients were switched due to resistance (as documented in medical notes), and 4 patients were switched due to intolerance or other reasons. The mutation type was captured in 6 patients, as described here.

[b] Resistance based on in vitro sensitivity (half maximal inhibitory concentration [IC_{50}]) as described in ELN 2013 (Baccarani *et al* 2013).

Supplementary Fig 1. TKI treatment pathways and molecular responses for patients with ELN-defined optimal, warning or failure responses while on second-line TKI



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Diabetes	3 (1)	3 (1)	0
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		Imatinib	Nilotinib	Imatinib	Nilotinib		1	0.4
		Imatinib	Nilotinib	Dasatinib	Imatinib		1	0.4
		Imatinib	Dasatinib	Nilotinib	Imatinib		1	0.4
		Imatinib	Bosutinib	Dasatinib	Imatinib		1	0.4
		Nilotinib	Imatinib	Dasatinib	Bosutinib		1	0.4
		Nilotinib	Imatinib	Bosutinib	Nilotinib		1	0.4
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5	L384M	Y	Imatinib	Nilotinib
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2L, second line; TKI, tyrosine kinase inhibitor.

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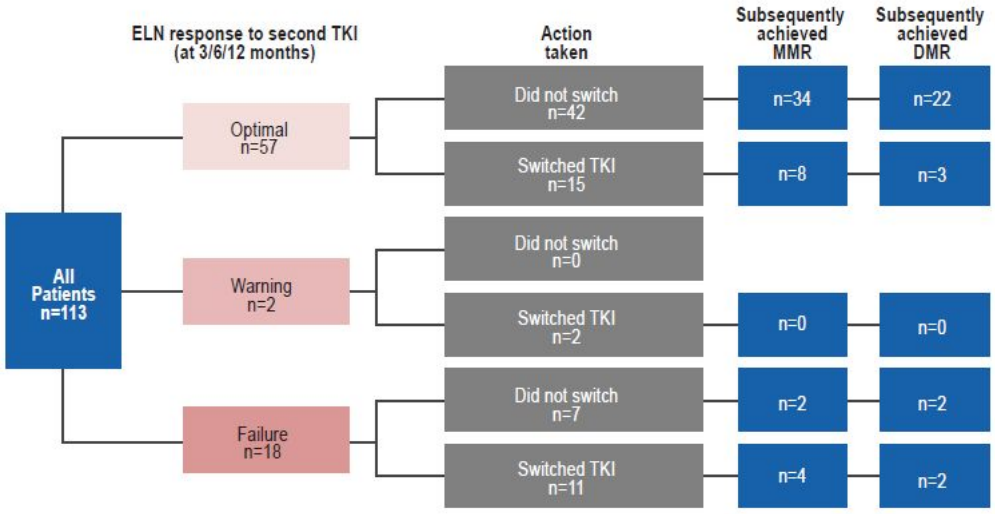

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Reviewer 1 major comments:

1. It is stated that patients receiving a 2G-TKI were younger than those receiving imatinib but what was median ages and range. Is there a statistical analysis attached to this observation.

Author Response: We have added clarification to the Results (page 7, lines 145-147 of the tracked changes version of our resubmission), as follows: *Patients receiving a first-line 2G-TKI were younger (median, 46 years [95% CI, 41-53 years]) than those receiving first-line imatinib (median, 55 years [95% CI, 52-59 years]; Mann-Whitney U test, P = 0.0128)*.

2a. For first-line TKI therapy category, what was the definition and split of patients that were defined as failure?

Author Response: We would like to draw the reviewer's attention to lines 184-185 on page 9, which provide the breakdown of reasons for switch, as follows: *Reasons for the first switch were resistance in 73 (65%), intolerance in 38 (34%) and other reasons in 2 (2%) (Supplementary Table III).* These reasons for switch were captured from patient notes, where resistance included any recorded failure, resistance, loss of response, lack of efficacy or loss of efficacy. This resistant group also included patients for whom both lack of efficacy and intolerance were documented as reasons for the switch. Intolerance was used to describe patients who switched purely for intolerance reasons (not lack of efficacy).

We have added further clarification to footnote c of Supplementary Table III (page 3 of the supplemental document), as follows: *Group classified as resistance based on documented failure, resistance or lack/loss of efficacy, including patients with resistance and patients with resistance and intolerance. The intolerance group included patients who switched for intolerance only.*

We have further clarified in the text that objectives included describing *recorded reasons for stopping/changing TKIs* (page 6, line 116).

For the ELN-defined milestones, we have further clarified the text (page 6, lines 126-127), as follows: *For comparison with ELN, where data were available, responses were categorised as optimal, warning or failure according to ELN 2013 recommendations (Baccarani* et al*, 2013)*.

The ELN-defined milestone of failure in first-line therapy (Figure 2) is defined as per ELN at 3, 6 and 12 months, within a 1-month window. We added clarification to footnote a of Figure 2 (pages 34-35, lines 638-641), as follows: *To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points (3, 6 and 12 months). In patients with multiple test results available, any patient with a failure response to first-line TKI at an ELN milestone (regardless of other responses achieved at earlier milestones) was classified as having a failure response*.

2b. What time points were used?

Author Response: ELN timepoints of 3, 6 and 12 months were used. We added this information to footnote a in Figure 2 for clarification (page 34, line 639).

2c. Were any failure time points pre-empted by ELN-defined warnings?

Author Response: To clarify the ELN-failure group, we have added footnote c to Figure 2 (page 35, lines 657-659), as follows: *Of 48 patients with ELN-defined failure responses, 39 were treated with imatinib as first-line therapy and 9 with a 2G-TKI; 38 patients (79%) also had an ELN-defined warning at a prior ELN time point (with either a molecular or cytogenetic test)*.

2d. Given the large proportion of patients without an evaluable molecular or cytogenetic test in the first year of therapy, how was this absent data managed.

Author Response: We would like to draw the reviewer's attention to the last two sentences of footnote a of Figure 2 (page 35, lines 644-644), which state the following: *Patients without assessments at any ELN milestone could not be categorized. Thirty-four patients had no evaluable test at any ELN milestone by either molecular or cytogenetic test*.

3. What was the definition of resistance in patients who switched TKI as the numbers who had failure to first-line TKI do not match the number of patients with resistance.

Author Response: We thank the reviewer for this comment. It is important here to distinguish between ELN-defined failure and switch of TKI due to resistance, as documented in the patient record. It is one of the interesting findings of our work that the two do not correlate, i.e., some patients with ELN-defined failure did not switch TKI, while some patients switched due to "resistance" (as documented in the patient record) even though the ELN criteria for treatment failure were not met. We have tried to clarify this important distinction in the text as described below.

We would like to draw the reviewer's attention to lines 184-185 on page 9, which provide the breakdown of reasons for switch, as follows: *Reasons for the first switch were resistance in 73 (65%), intolerance in 38 (34%) and other reasons in 2 (2%) (Supplementary Table III).* These reasons for switch were captured from patient notes, where resistance included any recorded failure, resistance, loss of response, lack of efficacy or loss of efficacy. This resistant group also included patients for whom both lack of efficacy and intolerance were documented as reason for the switch. Intolerance was used to describe patients who switched purely for intolerance reasons (not lack of efficacy).

We have added further clarification to footnote c of Supplementary Table III (page 3 of the supplemental document), as follows: *Group classified as resistance based on documented failure, resistance or lack/loss of efficacy, including patients with resistance and patients with resistance and intolerance. The intolerance group included patients who switched for intolerance only.*

We have further clarified in the text that objectives included describing *recorded reasons for stopping/changing TKIs* (page 6, line 116).

For the ELN-defined milestones, we have further clarified the text (page 6, lines 126-127), as follows: *For comparison with ELN, where data were available, responses were categorised as optimal, warning or failure according to ELN 2013 recommendations (Baccarani* et al*, 2013)*.

The ELN-defined milestone of failure in first-line therapy (Figure 2) is defined as per ELN at 3, 6 and 12 months, within a 1-month window. We added clarification to footnote a of Figure 2 (pages 34-35, lines 638-641), as follows: *To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points (3, 6 and 12 months). In patients with multiple test*

***results available, any patient with a failure response to first-line TKI at an ELN milestone (regardless of other responses achieved at earlier milestones) was classified as having a failure response*.**

To further clarify the ELN-failure group, we have added footnote c to Figure 2 (page 35, lines 657-659), as follows: *Of 48 patients with ELN-defined failure responses, 39 were treated with imatinib as first-line therapy and 9 with a 2G-TKI; 38 patients (79%) also had an ELN-defined warning at a prior ELN time point (with either a molecular or cytogenetic test)*.

4. For patients with intolerance, was there any data on dose modification/reduction prior to switch? How were these graded? Minor adverse events or serious adverse events such as pleural effusions, or cardiovascular events?

Author Response: We would like to clarify that adverse events were not collected as per the protocol in this study (page 6, lines 117-118). Therefore, although dose modifications were captured, allowing comparison between imatinib and 2G-TKIs, the reasons for dose modifications were not captured. We would like to draw the reviewer's attention to the following text on lines 173-175 (page 8) for clarification of level of reduction/modifications in first line: *For patients receiving imatinib or nilotinib, respective median starting doses were 400 or 600 mg/day; 24/203 (12%) and 8/50 (16%) had dose reductions, while 14% and 12% had dose interruptions.*

5. In Table 1 and 2, >90% of 2G-TKI patients were on nilotinib. Does it serve a purpose to split patients in nilotinib treated at all or is this redundant.

Author Response: We would like to highlight that choice of 2G-TKI is of specific interest based on baseline comorbidities, as dasatinib and nilotinib have distinct profiles.

6a. Table 4 needs to be reworked. Is the overall responses and first-line TKI responses not reporting the same thing? How are the denominators different if they are both looking at first-line TKIs?

Author Response: We would like to clarify that the analysis of overall response is an intention-to-treat type of analysis, which is based on first-line TKI but also includes data from later-line TKI treatment in patients who switched from their first-line TKI; in contrast, the analysis of first-line TKI response reflects responses observed on first-line TKI only.

We have added clarification to footnote c of Table IV (page 31, lines 601-602), which is now worded as follows: *The columns for overall response reported the duration of follow-up for all TKI therapies, including later-line TKIs in patients who switched from their first-line TKI (from start of first-line TKI to most recent data collection, akin to an intention-to-treat analysis). The columns for first-line TKI therapy reported the duration of follow-up for only first-line TKI therapy (from start of first-line TKI to most recent data collection or death in patients who continued receiving first-line TKI or to end of first-line TKI for patients who switched to a second-line TKI)*.

6b. What is the purpose of differentiating nilotinib patients from dasatinib patients when >90% are nilotinib treated.

Author Response: This demonstrates that observed outcome data were not skewed by the 4 dasatinib-treated patients and provides consistency in groupings from baseline (please see our response to Comment 5 above).

7a. Table 5 needs to be reworked. Is EMR in these patients assessing 3-month BCR-ABL1 levels after switching to the second-line agent or at 3 months of first-line TKI?

Author Response: Table V is a summary of molecular responses after switching to second-line TKI therapy. To provide clarity, we have edited footnote a of Table V (page 32, lines 611-615), which now reads as follows: *Molecular responses after switch to second TKI were assessed as EMR (BCR-ABL1^{IS} ≤10% at 3 months), MMR (BCR-ABL1^{IS} ≤0.1%) by 12 months, MMR at any time and DMR (BCR-ABL1^{IS} ≤0.01%) at any time*.

7b. Row 4 and 5 are confusing.

Author Response: To simplify Table V (page 32), we have removed row 4 (i.e., EMR at 3 months [±1 month] in patients with BCR-ABL1 at 3 months, n [%]), as this is not needed in addition to row 5.

Reviewer 1 minor comment:

1. In patients that had kinase domain mutations assessed, how many had actionable mutations?

Author Response: As detailed in the table below, all mutations recorded were clinically actionable. We have added this information as Supplementary Table VI (page 6 of supplemental document)

Supplementary Table VI. Summary of documented mutations[a]

Patient	Details	Actionable mutation (Y/N)	Resistance[b]	2L TKI
1	Q252H	Y	Imatinib	Nilotinib
2	E255V	Y	Imatinib and to lesser extent nilotinib, bosutinib	Dasatinib
3	T315I	Y	All TKIs except ponatinib	Ponatinib
4	E255K F359C	Y	Imatinib and to lesser extent nilotinib, bosutinib	Dasatinib
5	L384M	Y	Imatinib	Nilotinib
6	E255V	Y	Imatinib and to lesser extent nilotinib, bosutinib	Dasatinib

[a] Among 113 patients who switched TKI, 40% (45 of 113) had mutation detection done at any time before or after switching; 21% (24 of 113) had mutation analysis done before the first switch, and of those, 20 patients were switched due to resistance (as documented in medical notes), and 4 patients were switched due to intolerance or other reasons. The mutation type was captured in 6 patients as described here.

[b] Resistance based on in vitro sensitivity (half maximal inhibitory concentration [IC_{50}]) as described in ELN 2013 (Baccarani *et al* 2013).

Editor's comments:

1. Please let me have your rebuttal and an amended manuscript as soon as possible so that I can make a decision on publication. Please ensure that one copy clearly highlights all changes made (ie in bold).

Author Response: We have submitted a version of the manuscript with tracked changes in addition to providing a clean copy.

2. You must list the pages and lines which have been amended.

Author Response: We have included the relevant page and line numbers in our responses to each reviewer comment.

3. Please ensure that the correct gene symbol, as defined by the HGNC http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl), is used for all genes mentioned in your paper.

Author Response: We have used this format for all genes mentioned in the manuscript.

4. Please quote your manuscript number and email address on all correspondence.

Author Response: We have included both the manuscript number and email address at the top of this letter.

5. Please submit an electronic version of each figure in either TIFF or EPS format, at a recommended resolution of 600 dpi, according to the information given at http://www.blackwellpublishing.com/authors/ digill.asp

Author Response: We have ensured that the submitted figures are in the correct format and resolution.

6. If you have not already done so, please could you provide five suitable keywords, and a short title of up to 60 characters and spaces.

Author Response: We have included a running title on the title page (page 1, line 5) and 5 key words below the abstract (page 3, lines 61-62).

7. Please also make sure your manuscript is in the correct format for this journal; failure to do so may DELAY the processing of your paper. BJH uses the HARVARD system of referencing: citations in the text take the form of author names and dates (e.g. Smith et al. 1990).).

Author Response: We have followed this format for the manuscript.

8. All references should be brought together at the end of the paper in ALPHABETICAL ORDER, with all AUTHORS, titles and TITLES OF JOURNALS spelt out in full, with both first and last page numbers given. REFERENCES MUST NOT BE NUMBERED.

Author Response: All references have been placed at the end of the manuscript in alphabetical order and not numbered. Titles of journals are spelled out, and first and last page numbers are included.

9. We also need full postal address, phone and fax numbers.

Author Response: We have provided full postal address and phone and fax numbers as requested.